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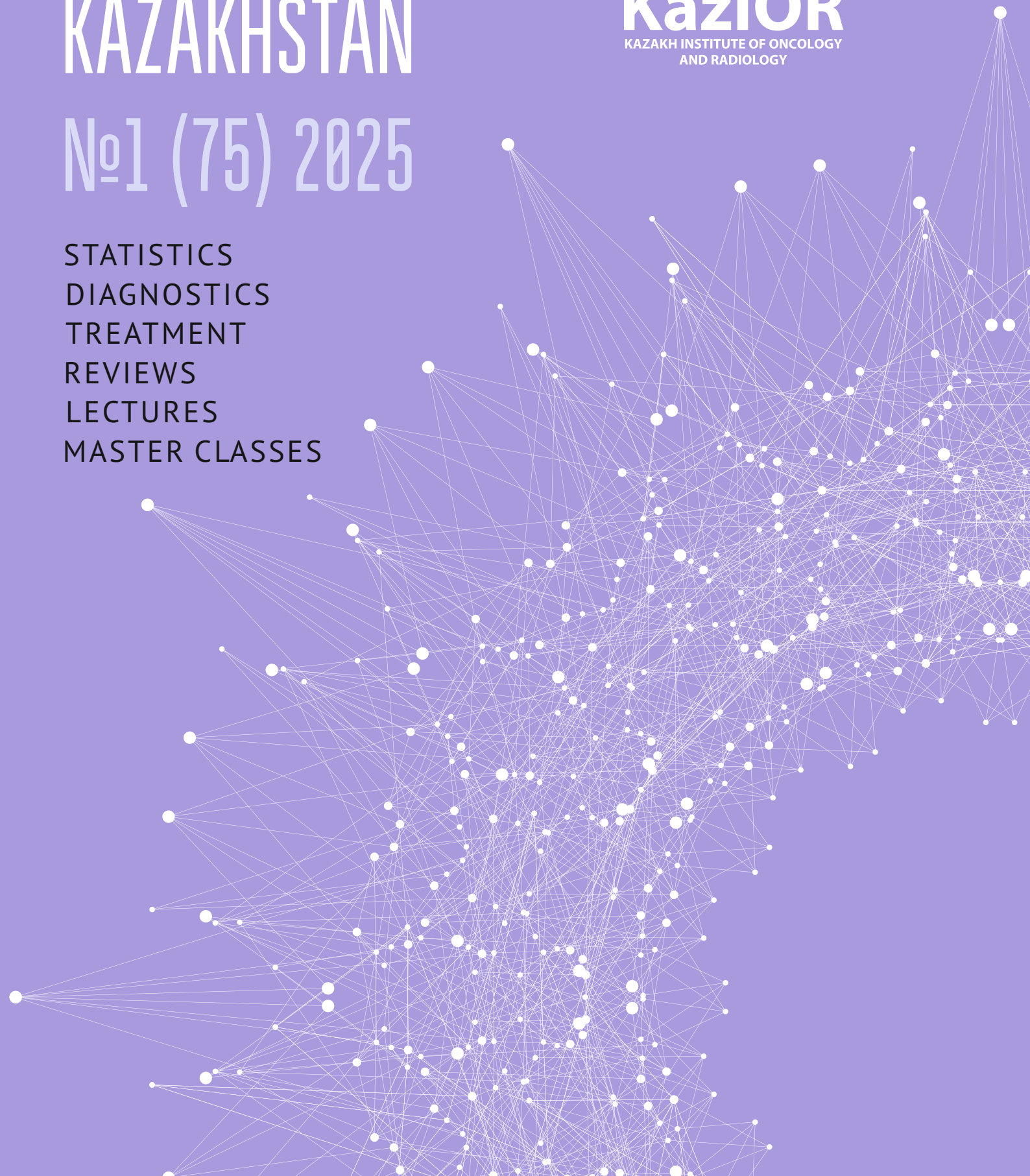

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Dear readers!

We are pleased to welcome you to the pages of the journal "Oncology and Radiology of Kazakhstan" spring issue"!

On behalf of the editorial staff, I would like to congratulate you on the arrival of the spring holidays and the renewal that the new season brings.

2025 continues to bring innovation and progress in oncology and radiology. We are confidently moving towards introducing new technologies, improved diagnostics and treatment, and stronger collaboration in our professional community. The current issue presents the results of interesting and relevant studies, such as "Assessment of oxygen extraction, lactate levels, central venous oxygen partial pressure, and venous-arterial carbon dioxide difference in oncological patients during blood transfusion," "Dynamic assessment of quality of life associated with visual impairment in patients receiving chemotherapy," and "Study of the oncological process influence on ovarian reserve."

We try to make each new issue of our Journal useful and informative for specialists in oncology and radiology. The articles presented in this issue rely on the latest scientific research and practical recommendations that help improve the quality of medical care.

This year, we will continue to improve content quality, expand our audience, and strengthen our community. May the current year inspire you for new achievements, success in your professional activities, and confidence in the future. We wish you health, happiness, and great achievements!

Respectfully Yours,
Dilyara Kaidarova,
Editor-in-Chief of the "Oncology and Radiology of Kazakhstan" journal

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OVARIAN CANCER INCIDENCE AND MORTALITY IN THE CITY OF ALMATY, 2014-2023

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ABSTRACT

Relevance: *According to the National Cancer Registry of Kazakhstan, the incidence of ovarian cancer in Almaty in 2023 was 18.3 per 100,000 women, and the mortality rate was 3.9 per 100,000 women. The overall survival rate for ovarian cancer (OC) in Almaty in 2023 was 53.7%. Currently, Almaty is among the regions with a high incidence of cancer and mortality.*

The study aimed to *assess changes in the incidence and mortality of OC among Almaty residents and the five-year survival of patients with OC from 2014 to 2023.*

Methods: *The changes in the structure and dynamics of morbidity and mortality from OC in Almaty over ten years (2014-2023) were analyzed based on the official accounting and reporting documentation. Statistical information processing was carried out using the SPSS software, version 23.0.*

Results: *From 2014 to 2023, the incidence rate increased from 14.2 to 18.3 per 100,000 women, while the mortality rate remained consistently low, at 3.9 per 100,000 women in 2023. In 2014, 127 cases of ovarian cancer were detected, of which 44.8% were at stages I and II of the disease. In 2023, 228 cases of ovarian cancer were registered, with stages I and II accounting for 52.2%.*

The frequency of new cases has significantly increased in recent years, starting at 50-54 years old and peaking at 55-59 years old. The highest incidence of OC shifted from 50-54 years old in 2014 to 55-59 years old in 2023.

Conclusion: *The study demonstrated significant advancements in diagnosing and treating ovarian cancer in Almaty, including reduced mortality rates and a higher proportion of early detections. However, further improvements in diagnostic methods, enhancing oncological awareness among primary care physicians, and increasing the average life expectancy of Almaty residents remain key priorities.*

Keywords: *ovarian cancer, incidence, mortality, Almaty.*

Introduction: According to Globocan 2020 statistical data, ovarian cancer (OC) is the eighth most common malignant disease among women and remains one of the leading causes of mortality in the field of gynecology [1]. In 2020, 313,959 new cases were reported, with 80% of cases being detected in the late stages of the disease, which worsens the prognosis [1]. Despite the development of surgery and chemotherapy, the 5-year survival rate remains as low as about 40% [2]. Further increases in incidence (up to 371,000 new cases) and mortality (up to 271,000 cases) are expected [1], emphasizing the need for a personalized approach to treatment.

About 1,000 new OC cases are registered in Kazakhstan annually, 2.9% of all cancer cases. The number of cases has increased by 21% in the last 15 years, and the mortality rate is 4.7 per 100,000 women. There is no routine testing for BRCA1 and BRCA2 gene mutations in the country yet, although their detection could significantly affect the treatment and prognosis of the disease [3].

OC is one of the most aggressive malignant diseases of the female reproductive system. High mortality is associated with late diagnosis, resistance to chemotherapy, and frequent relapses. Effective diagnostic methods, screening, and personalized approaches are needed to improve survival [4]. Standard treatment includes surgical removal of the tumor and chemotherapy with platinum drugs. However, the lack of reliable prognostic biomarkers makes it difficult to choose the optimal strategy [5]. Modern genetics and molecular profiling research has led to new therapies to reduce relapses and side effects. Genetic testing for BRCA1/2 mutations has already become the standard for patients with epithelial OC. It allows for selecting individualized therapy and improving prognosis [6].

Maintenance therapy with PARP inhibitors, bevacizumab, and drugs affecting homologous recombination deficiency is becoming more common. In parallel, actively developing immune therapy opens up new treatment options [7]. According to the 2020 WHO classification, OC is a heterogeneous group of tumors, 90% of which are epithelial tumors. Among them, high-grade serous carcinoma (HGSC) is the most common and aggressive, accounting for 70% of all cases [8].

OC is the third most common cancer in women after breast and lung cancer [9]. This emphasizes the need for further study of the disease and the search for more effective methods of diagnosis and treatment.

The study aimed to assess changes in the incidence and mortality of OC among Almaty residents and the five-year survival of patients with OC from 2014 to 2023.

Materials and Methods: The analysis of changes in the structure and dynamics of OC incidence and mortality in the city of Almaty for the ten years (2014-2023) was carried out based on official accounting and reporting documentation data. The object of the study was 1,472 women who newly diagnosed with OC during the specified period. The source of data was the control cards of case follow-up (account form 030-6/u).

Data from the International Classification of Diseases 10th revision (ICD-10) on tumor localization, information from the National Cancer Registry (Electronic Register of Cancer Patients) on malignant neoplasms, official reports of oncology centers of the Republic of Kazakhstan, including the Report on Malignant Neoplasms Diseases (account form No. 7) for 2014-2023, as well as cards of patients firist diagnosed with malignant neoplasms (account form 090/U) were used for epidemiological analysis. Additionally, the data of the Agency of the Republic of Kazakhstan on demographic indicators, including the number and sex-age structure of the population of Almaty for the study period, were analyzed.

Results: When analyzing crude and intensive markers of OC incidence, a tendency to increase the frequency of registration of this disease from 2014 to 2023 was revealed (Figure 1). The analyzed statistical data confirms the International Agency for Research on Cancer's forecasts predicting a global increase in new OC cases [10]. In 2014, the incidence was 14.2 cases per 100,000 women, while by 2023, the rate had increased to 18.3 per 100,000. The maximum incidence level was registered in 2023, with 18.3 cases per 100,000 female population. According to the National Cancer Registry, 228 new cases were identified in Almaty in 2023. At the same time, OC mortality has decreased during the study period. Sixty-one fatal cases registered in 2014 corresponded to a rate of 6.8 per 100,000 women. In 2023, this rate decreased to 3.9 per 100,000, with 49 deaths (Figure 1).

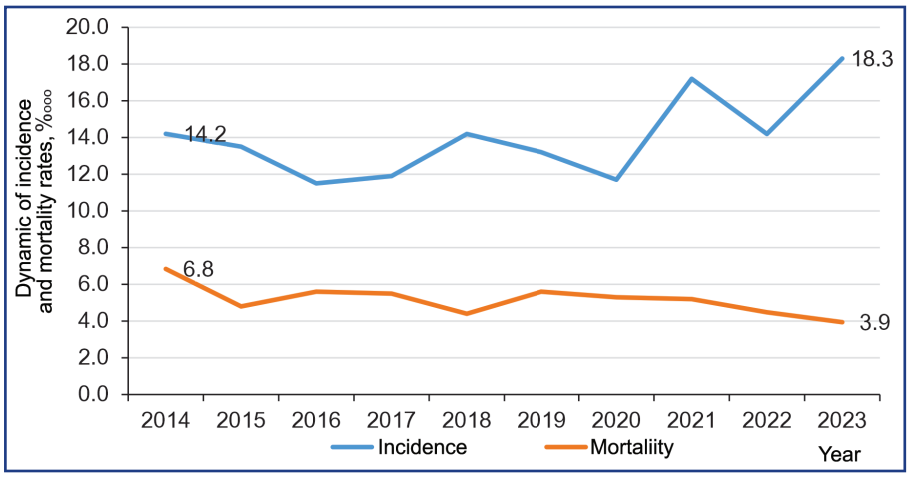

Figure 1 – Dynamics of ovarian cancer incidence and mortality in Almaty (2014-2023) per 100,000 female population

Analysis of registration of new ovarian cancer cases in different age groups revealed an increase in incidence among middle-aged and older women in 2023 compared to 2014 (Figure 2). A significant rate increase is associated with expanded diagnostic capabilities and life expectancy in Kazakhstan [11].

The increasing incidence of OC among middle-aged and older women emphasizes improving diagnostic measures and strengthening surveillance during periodic health examinations in outpatient clinics (Figure 2). Analysis of the age distribution of cases for 2014 and 2023 (absolute indicators) showed an increase in newly detected cases in those age groups. Stage analysis at diagnosis showed a tendency for more frequent detection of OC at stages I and III during the analyzed period (Figures 3 and 4). In 2014, 127 OC cases were registered, with 44.9% of patients having stage I-II disease. In 2023, the number of cases increased to 228, and the share of Stages I-II cases was 52.2%. Stage III was registered in 49.6% of detected cases in 2014 and 44.3% in 2023. The frequency has doubled for Stage I cases at diagnosis and increased by half for Stage III cases. At that, the number of neglected cases (stage IV at detection) has not significantly increased.

Table 1 presents key statistical indicators reflecting the effectiveness of oncologic care for OC patients in Almaty. The number of new cases increased by 228 (55.7%) in 2023 compared to 2014. In 2023, morphologic confirmation of the diagnosis was obtained in 53.9% of cases. According to the Cancer Registry, 52.2% of the cases were detected early, while 49.5% were diagnosed during periodic health examinations. During the analyzed period, early detection rates have increased significantly due to improvements in diagnostic methods and increased oncological vigilance among primary care gynecologists. In addition, one-year ovarian cancer mortality decreased to 5.7% in 2023 compared to 14.1% in 2014, showing a positive trend and

a more than twofold reduction of this rate. This achievement is connected with the introduction of modern diagnostic methods, improved treatment quality, and new therapeutic approaches. In 2023, the number of patients under observation increased to 1,257, with 53.7% registered for 5 years or more.

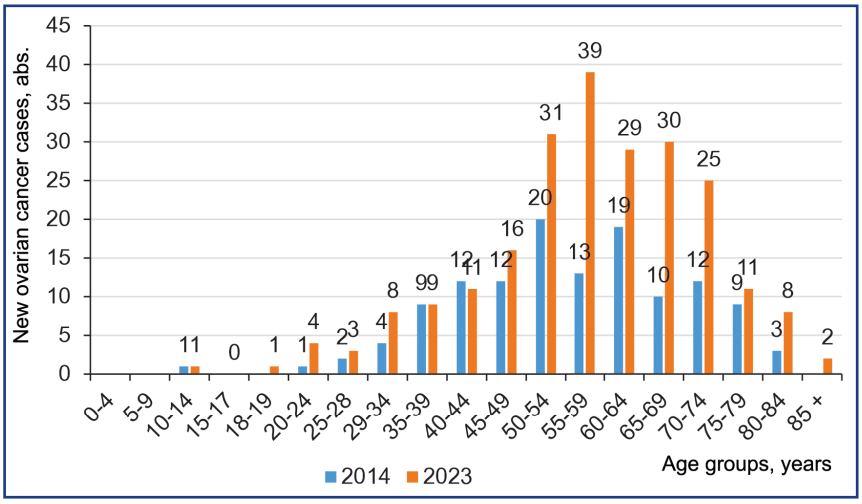

Figure 2 – Number of new ovarian cancer cases in different age groups in 2014 and 2023 (absolute indicators)

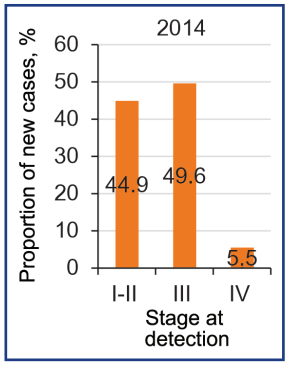

Figure 3 – Distribution by stage of specific weight of first diagnosed ovarian cancer cases in Almaty women in 2014 (%)

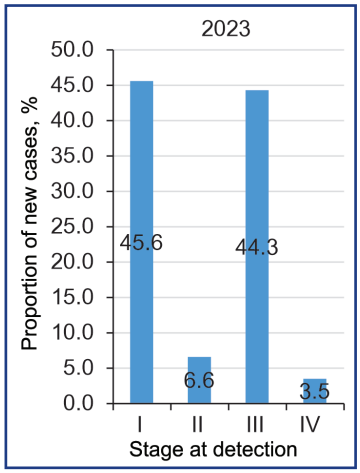

Figure 4 – Distribution by stage of first diagnosed ovarian cancer cases in Almaty women in 2023 (%)

Table 1 – Dynamics of statistical indicators of ovarian cancer incidence and mortality in Almaty (2014 and 2023)

Indicators	2014	2023
New cases, n	127	228
Morphologically verified diagnosis, % (n)	89,7 (114)	53.9 (123)
Cases diagnosed at stages I and II, % of detected cases	44.8	52.2
Incidence (crude intensive rate) per 100,000 population	14.2	18.3
Mortality (crude intensive rate) per 100,000 population	6.8	3.9
Diagnosed at stage III, % of detected cases	49.6	44.2
Detected at stages I and II during periodic health examinations, n (new cases)	0.78 (1)	49.5 (113)
Survivors for less than one year after diagnosis, among those registered in the previous year (one-year mortality), n (%)	14.1 (18)	5.7 (13)
Number of registered by the end of the year, n	690	1257
Number of patients on record for 5 years or more, n	354	676

Discussion: Over the past 10 years, there has been an increase in ovarian cancer incidence in Almaty. The incidence rate increased from 14.2 per 100,000 female population in 2014 to 18.3 per 100,000 female population in 2023. This trend is connected with the improvement of diagnostic methods, increased oncological vig-

ilance of primary care gynecologists, and the increase in the average life of Almaty residents. Despite the lack of justified screening programs to detect ovarian cancer, early diagnosis using preferred methods such as ultrasound plays a key role in detecting ovarian cancer at early stages [12].

In contrast, OC mortality has decreased from 6.8 cases per 100,000 females in 2014 to 3.9 in 2023. This could be due to the introduction of modern treatment methods, including chemotherapy and targeted therapy, and the increasing availability of medical care.

OC is the sixth in the structure of female cancer incidence in Almaty. Over the last 10 years (2014-2023), 1,472 new cases and 534 deaths caused by this pathology were registered.

The growing number of reported OC cases in middle and elderly age indicates the need to strengthen preventive measures in these age groups. Older women should be especially monitored because the risk of OC developing increases with age. For 2023, the maximum OC incidence has shifted from age 50-54 years to age group 55-59 years compared to 2014.

A positive trend during the analyzed period was an increased early detection of patients with OC stages I and II, from 44.8% in 2014 to 52.2% in 2023. The increase in stage I diagnosis is particularly notable, indicating progress in early disease detection. At the same time, the proportion of patients with stage III and neglected stage IV has decreased from 49.6% in 2014 to 44.2% in 2023. This suggests that women are increasingly seeking medical attention earlier in the disease process.

The factors that influenced the results are improved diagnostics by introducing modern imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), as well as laboratory tests.

Ovarian cancer remains one of the most challenging problems in oncology due to the lack of pronounced symptoms at the early stages. Increased doctors' vigilance has played a significant role in improving the detection and treatment of the disease and creating an environment that encourages women to take a conscious and responsible approach to preventive examinations. Improving the medical system, including the availability of oncology centers, introducing modern technologies, and improving the quality of medical care have also become important aspects. Improvement of ovarian cancer diagnosis and treatment methods, including the use of modern technology and personalized therapy approaches, is needed to further improve the situation. The population should also be actively informed about this disease's early signs and risk factors to increase the likelihood of timely detection.

Conclusion: The study's results indicate significant progress in improving the diagnosis and treatment of ovarian cancer in Almaty. This has reduced mortality rates and increased the proportion of cases detected at early stages. However, the task of further improvement of preventive measures, introduction of more accurate and accessible diagnostic methods, and increase in oncologic vigilance among primary care gynecologists remains relevant. These steps aim to improve patients' quality of life and increase duration.

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АҢДАТПА

2014-2023 ЖЫЛДАРДАҒЫ АЛМАТЫ ҚАЛАСЫНДАҒЫ АНАЛЫҚ БЕЗДІҢ ҚАТЕРЛІ ІСІГІМЕН СЫРҚАТТАНУШЫЛЫҚ ЖӘНЕ ӨЛІМ-ЖІТІМ

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Өзектілігі: *Ұлттық канцер-тіркелімнің деректері бойынша Алматы қаласында (Қазақстан) аналық бездің катерлі ісігімен (АБҚІ) сырқаттанушылық деңгейі 2023 жылы 100 000 әйелге шаққанда 18,3, өлім — жітім деңгейі 100 000 әйелге шаққанда 3,9 құрайды. Алматыда 2023 жылы АБҚІ-мен өмір сүрудің жалпы деңгейі 53,7%-ды құрады. Қазіргі уақытта Алматыда АБҚІ-нен сырқаттанушылық пен өлім-жітім деңгейі жоғары өңірлердің бірі болып табылады.*

Зерттеу мақсаты: *Алматы тұрғындары арасында АБҚІ-мен сырқаттанушылық пен өлім-жітім деңгейінің өзгеруін, сондай-ақ 2014-2023 жж. осы диагнозы бар пациенттердің бес жылдық өмір сүру көрсеткіштерін бағалау.*

Әдістері: *Алматы қаласында он жылдық кезеңдегі (2014-2023 жж.) сырқаттанушылық пен өлім-жітімнің құрылымы мен динамикасындағы өзгерістерді талдау есепке алу-есеп беру құжаттамасының деректері негізінде жүргізілді. Ақпаратты статистикалық өңдеу SPSS 23.0 бағдарламалық жасақтамасын қолдану арқылы жүзеге асырылды.*

Нәтижелері: *2014-2023 жылдары 100 000 әйелге шаққанда 14,2-ден 18,3-ке дейін сырқаттанушылық деңгейінің өсуі байқалды, бұл ретте өлім-жітім деңгейі тұрақты төмен болып қалады және 2023 жылы 100 000 әйелге шаққанда 3,9 құрады. 2014 жылы АБҚІ-нің 127 жағдайы анықталды, оның 44,8%-ы аурудың I және II сатыларында болды. 2023 жылы АБҚІ-нің 228 жағдайы тіркелді, оның I және II кезеңдері 52,2% құрады.*

Соңғы жылдары 50-54 жас тобынан бастап 55-59 жас тобында ең көп кездесетін АБҚІ-нің жаңа жағдайларын тіркеу жиілігінің айтарлықтай өсуі байқалды. 2023 жылы 2014 жылмен салыстырғанда АБҚІ-нің ең жоғары деңгейі "50-54 жас" тобынан "55-59 жас" тобына ауысты.

Қорытынды: *зерттеу нәтижелері Алматы қаласында АБҚІ диагностикасы және емдеу жөніндегі іс-шаралардың жақсаруы елеулі жетістіктерге: өлім-жітімнің төмендеуіне және аурудың ерте сатысында анықталған жағдайлардың үлесінің ұлғаюына әкелгенін көрсетеді. Алайда диагностика әдістерін жетілдіру, алғашқы медициналық-санитарлық көмек дәрігерлерінің онкологиялық қырағылығын арттыру, сондай-ақ Алматы қаласы тұрғындарының орташа өмір сүру ұзақтығын арттыру маңызды міндеттер болып қала береді.*

Түйінді сөздер: *аналық бездің катерлі ісігі (АБҚІ), сырқаттанушылық, өлім-жітім, Алматы.*

АННОТАЦИЯ

ЗАБОЛЕВАЕМОСТЬ И СМЕРТНОСТЬ ОТ РАКА ЯИЧНИКОВ В ГОРОДЕ АЛМАТЫ ЗА 2014-2023 гг.

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Актуальность: *По данным Национального канцер-регистра, уровень заболеваемости раком яичников (РЯ) в городе Алматы (Казахстан) на 2023 год составляет 18,3 на 100 000 женщин, уровень смертности – 3,9 на 100 000 женского населения. Общий уровень выживаемости при РЯ в Алматы на 2023 год составил 53,7%. В настоящее время Алматы является одним из регионов с высоким уровнем заболеваемости и смертности от РЯ.*

Цель исследования *– оценка изменений уровня заболеваемости и смертности от рака яичников среди жителей Алматы, а также показателей пятилетней выживаемости пациентов с данным диагнозом за 2014-2023 гг.*

Методы: *Анализ изменений в структуре и динамике заболеваемости и смертности от РЯ в городе Алматы за десятилетний период (2014-2023 гг.) проведен на основе данных учётно-отчётной документации. Статистическая обработка информации осуществлялась с применением программного обеспечения SPSS версии 23.0.*

Результаты: *В 2014-2023 гг. отмечен рост уровня заболеваемости с 14,2 до 18,3 на 100 000 женщин, при этом уровень смертности остаётся стабильно низким и в 2023 году составил 3,9 на 100 000 женщин. В 2014 году было выявлено 127 случаев РЯ, из которых 44,8% приходились на I и II стадии заболевания. В 2023 году зарегистрировано 228 случаев РЯ, причём на I и II стадии приходилось 52,2%.*

В последние годы отмечается значительное увеличение частоты регистрации новых случаев РЯ, начиная с возрастной группы 50-54 лет, с пиком в группе 55-59 лет. В 2023 году по сравнению с 2014 годом наибольший уровень заболеваемости РЯ сместился из возрастной группы «50-54 года» в группу «55-59 лет».

***Заключение:** Результаты исследования показывают, что улучшение мероприятий по диагностике и лечению РЯ в городе Алматы привело к значительным достижениям: снижению смертности и увеличению доли случаев, выявленных на ранних стадиях заболевания. Однако остаются важными задачами совершенствование методов диагностики, повышение онкологической настороженности врачей первичной медико-санитарной помощи, а также увеличение средней продолжительности жизни жителей города Алматы.*

***Ключевые слова:** рак яичников (РЯ), заболеваемость, смертность, Алматы.*

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ASSESSMENT OF OXYGEN EXTRACTION, LACTATE LEVELS, CENTRAL VENOUS OXYGEN PARTIAL PRESSURE, AND VENOUS-ARTERIAL CARBON DIOXIDE DIFFERENCE IN ONCOLOGICAL PATIENTS DURING BLOOD TRANSFUSION

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ABSTRACT

Relevance: *Anemia is a common hematologic syndrome, particularly among oncological patients, where its prevalence ranges from 40% to 90%, depending on treatment. Blood transfusion remains the primary method of anemia correction; however, hemoglo-bin (Hb) level remains the sole criterion for transfusion decisions despite not always accurately reflecting tissue oxygen demand. Consequently, alternative physiological transfusion triggers are being actively studied, including oxygen extraction ratio (O_2ER), central venous oxygen partial pressure (PvO_2), lactate (Lac), and venous-to-arterial carbon dioxide difference (ΔCO2).*

The study aimed to *assess the effect of blood transfusion on O_2ER, PvO_2, Lac, and ΔCO_2 in oncological patients with anemia and determine their potential as physiological transfusion triggers.*

Methods: *A prospective observational study included 107 oncological patients with anemia requiring blood transfusion. Arterial and central venous blood samples were collected before and 1 hour after transfusion to assess Hb, PvO_2, Lac, O_2ER, and ΔCO_2. Statistical analysis was performed using the Wilcoxon test and Spearman's rank correlation coefficient.*

Results: *After blood transfusion, a statistically significant improvement in key parameters was observed:*

- *O_2ER decreased from 35.4% (31.8; 41.9) to 29.3% (26.0; 33.4) ($p<0.001$);*
- *PvO_2 increased from 34.8 (32.7; 38) to 36 (34; 39) mmHg ($p=0.005$);*
- *ΔCO_2 decreased from 7 (5.2; 8.6) to 6.3 (4.9; 7.7) mmHg ($p=0.004$);*
- *Lac changed slightly from 1.1 (0.9; 1.7) to 1.0 (0.6; 1.55) mmol/L ($p=0.005$), remaining within the normal range.*

Correlation analysis revealed that PvO_2, ΔCO_2, and Lac were significantly associated with baseline O2ER levels but did not correlate with baseline Hb levels ($p>0.05$). This confirms that the Hb level does not accurately reflect oxygen delivery needs, whereas alternative physiological markers may serve as more reliable transfusion decision criteria.

Conclusion: *Changes in O_2ER, PvO_2, and ΔCO_2 after blood transfusion suggest their potential use as physiological transfusion triggers. Unlike the Hb level, these parameters more accurately reflect oxygen delivery changes. Although lactate correlated with baseline Hb, it cannot serve as a reliable transfusion trigger in this patient population, as its levels remained within the normal range. Further research is needed to define threshold values for physiological transfusion triggers and evaluate their impact on clinical outcomes.*

Keywords: *blood transfusion, anemia, oxygen extraction.*

Introduction: Anemia is one of the most common hematologic syndromes in clinical practice. At the same time, anemia in cancer patients occurs in more than 40% of cases, and in patients receiving chemotherapy, the incidence of anemia can reach up to 90% [1]. Anemia is an independent factor that worsens clinical outcomes in various groups of patients [1, 2]. One of the main methods of anemia treatment is a blood transfusion. In modern transfusion practice, a distinction is made between restrictive and liberal transfusion strategies. The liberal strategy involves transfusion of red blood cell components at higher hemoglobin levels. In turn, the restrictive strategy is based on minimizing transfusions. It involves prescribing blood transfusion only when lower hemoglobin levels are reached, which is aimed at reducing the risk of possible complications [3], such as volume overload, transfusion reactions, and the immunomodulatory effect of blood transfusions. The restrictive strategy is the basis for many modern recommendations for the transfusion erythrocyte-containing blood components, including the current order of the Ministry of Health of the Republic of Kazakhstan [4-8].

The hemoglobin level is the key criterion for deciding on blood transfusion. In this regard, the hemoglobin level cannot reflect the level of oxygen delivery, and increasing the latter is the main goal of blood transfusion therapy. That is why several studies show the benefits of a liberal transfusion strategy and improved clinical outcomes in patients with higher hemoglobin levels [9-11]. This is primarily indicated for patients with limited reserves for physiological compensation of reduced oxygen delivery, including those

with cardiovascular pathologies or elderly patients. A similar situation was shown in a study by P. de Almeida et al.: a liberal strategy improved the clinical outcomes in cancer patients after major surgical interventions [12]. These data also demonstrate the imperfection of hemoglobin as the only trigger for blood transfusion. In connection with this, relevant alternative physiological triggers for blood transfusion have been actively studied in recent years, which makes it possible to more accurately assess the patient's need for transfusion. These include the oxygen extraction coefficient (O_2ER), arteriovenous difference in carbon dioxide partial pressure (ΔCO_2), central venous blood saturation ($ScvO_2$), lactate (Lac), central venous oxygen partial pressure (PvO2), and other markers of oxygen delivery and tissue hypoxia. This study analyzed the effect of blood transfusion on O_2ER, ΔCO_2, Lac, PvO2 in cancer patients with anemia.

The study aimed to assess the effect of blood transfusion on O_2ER, PvO_2, Lac, and ΔCO_2 in oncological patients with anemia and determine their potential as physiological transfusion triggers.

Methods: A prospective observational study included 107 oncological patients. The main inclusion criteria were:

– anemia requiring blood transfusion;

– presence of a central venous catheter.

The exclusion criteria were:

– respiratory support (invasive/non-invasive ventilation, high-flow oxygen therapy);

– vasopressor and/or inotropic support;

– shock of any etiology;

– childhood;

– pregnancy.

The study included patients over 18 years of age, 66 (61.7%) women and 41 (38.3%) men. The median age of patients was 57 (46–65) years.

All patients received the packed red blood cell (PRB) transfusion, which triggered the hemoglobin level. Before and 1 hour after blood transfusion, the hemoglobin (Hb) levels, PvO_2, Lac have been measured.

$$O_2ER \text{ calculated as } [(CaO_2\text{-}CcvO_2)/CaO_2*00\%]. \quad (1)$$

$$\Delta CO_2 \text{ calculated as } PvCO_2\text{-}PaCO_2. \quad (2)$$

Central venous blood was taken from the central venous catheter located in the basin of the superior vena cava (subclavian or internal jugular vein), and arterial blood was taken from the radial artery.

The statistical analysis and visualization of the data obtained were carried out using the R 4.3.1 statistical software framework (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics for categorical variables are presented as absolute and relative frequencies (n (%)), and for quantitative variables, they are presented as a median (1-3rd quartile). For comparison of quantitative indicators before and after the intervention, the Wilcoxon signed-ranks test for matched pairs has been used. The Spearman's rank correlation coefficient (ρ) with a corresponding 95% confidence interval (95% CI) has been used to estimate the direction and strength of the association between quantitative variables. The association was considered statistically significant at $p<0.05$.

Results: The median hemoglobin concentration before transfusion was 73 (64.5; 78) g/L. After transfusion, the median hemoglobin increased to 85 (76.5; 93.7) g/L. The median elevation of hemoglobin after transfusion amounted to 13 (8.5; 21) g/L and was statistically significant ($p<0,001$).

The main diagnosis in all patients included in the study (n=107) was malignant neoplasms. The most common were tumors of the gastrointestinal tract – in 30 patients (28.0%), and malignant neoplasms of bones and soft tissues were detected in 30 patients (28.0%). Tumors of the female reproductive system were detected in 22 patients (20.6%), tumors of the chest organs in 8 patients (7.5%), and neoplasms of the head and neck in 4 patients (3.7%). Malignant tumors of the urinary system and male genital organs were diagnosed in 8 patients (7.5%). Primary multiple cancers were detected in 3 patients (2.8%) and other malignant tumors in 2 patients (1.9%). A brief clinical and demographic description of the enrolled patients is presented in Table 1.

The effect of blood transfusion and the dynamics of O_2ER changes in response to transfusion are presented in Figure 1.

Oxygen extraction: The level of O_2ER before blood transfusion was higher than the normative values and composed 35.4% (31.8; 41.9). After the blood transfusion, the median level of oxygen extraction was 29.3% (26%; 33.4%). Concurrently, a statistically significant normalization of the O_2ER level after transfusion of erythrocyte-containing media has been observed: the median decline in O_2ER after transfusion amounted to 5.8% (-10.7%; -1%) ($p<0.001$). The median O_2ER value before blood transfusion was higher than the normative values, and the transfusion led to the normalization of this indicator. The effect of blood transfusion and the dynamics of O_2ER changes in response to transfusion are presented in Figure 1.

Partial pressure of oxygen in central venous blood: The median level of PvO_2 before blood transfusion was 34.8 (32.7; 38) mmHg. After the blood transfusion, a statistically significant elevation of the partial pressure of oxygen in the central venous blood has been recorded - 36 (34-39) mmHg. The median change of PvO_2 after transfusion composed 1.2 (-1.35; 3) mmHg ($p=0.005$). The effect of blood transfusion and the dynamics of changes in PvO_2 indicator in response to transfusion are presented in Figure 2.

Table 1 – Clinical and demographic characteristics of the enrolled patients

Indicator	Value
Age (years), median (min; max)	57 (46; 65)
Sex, n 107 (100%)	
Female	66 (61.7%)
Male	41 (38.3%)
Body mass index (kg/m²), median (min; max)	23,9 (21; 26,7)
Type of anemia, n 107 (100%)	
Acute	71 (66,4%)
Chronic	36 (33,6%)
Tumor localization, n 107 (100%)	
Bones and soft tissues	30 (28,0%)
GIT	30 (28,0%)
Female genitalia	22 (20,6%)
Urinary system and male genital organs	8 (7,5%)
Chest organs	8 (7,5%)
Head and neck	4 (3,7%)
Primary multiple cancer	3 (2,8%)
Other tumors	2 (1,9%)
Concomitant diseases, n 107 (100%)	
Arterial hypertension	34 (31,8%)
Coronary heart disease	14 (13.1%)
Obesity	13 (12,2%)
Type 2 diabetes mellitus	10 (9,3%)
Cerebrovascular diseases	3 (2,8%)
Other	85 (79,4%)
Apache II Severity Rating Scale, Median (min; max)	12 (11; 14)
Transfusion volume, median (min; max)	340 (310; 410)

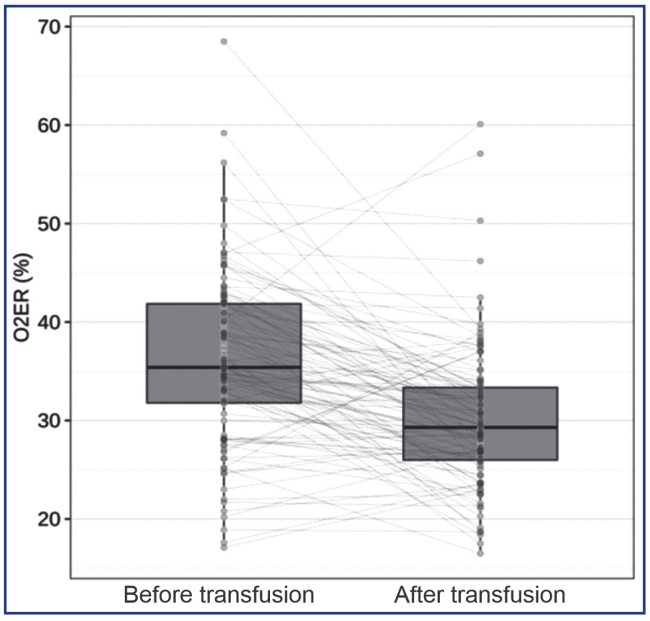

Figure 1 – O_2ER level before and after blood transfusion

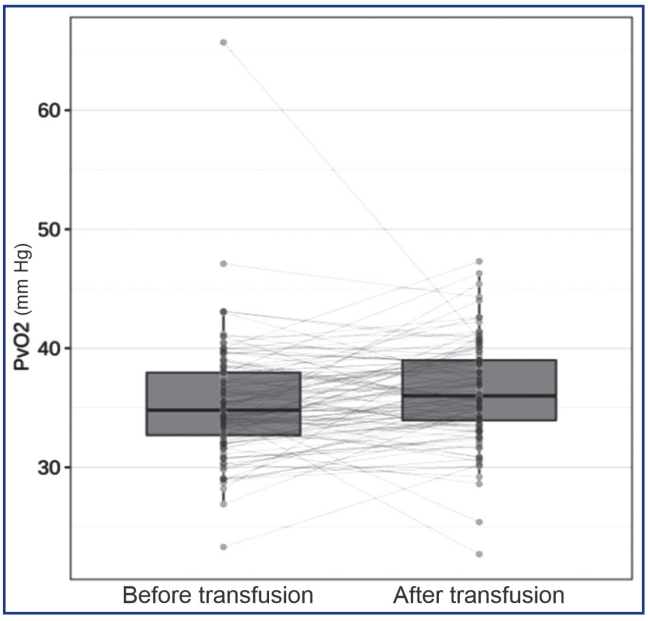

Figure 2 – PvO_2 level (mmHg) before and after blood transfusion

Lactate: The median lactate concentration amounted to 1.1 (0.9; 1.7) mmol/L before blood transfusion and 1 (0.6; 1.55) mmol/L after the blood transfusion; the median change in lactate levels in response to blood transfusion was -0.1 (-0.45; 0.1) mmol/L. Even though the median lactate concentration was within the normative values before and after blood transfusion, the change in lactate levels in response to blood transfusion was statistically significant (p=0.005). The lactate levels before and after blood transfusion are presented in Figure 3.

Venoarterial difference in carbon dioxide (ΔCO_2) levels: The median ΔCO_2 pre-transfusion level was higher than the normative level 7 (5.2; 8.6) mmHg. After the blood transfusion, the level of ΔCO_2 changed statistically significantly towards normalization; the median ΔCO_2 decline was -0.9 (-2.4; 0.8) mmHg. The ΔCO_2 median after transfusion composed 6.3 (4.9; 7.7) mmHg (p=0.004) (Figure 4). The level of ΔCO_2 before and after blood transfusion is presented in Figure 4.

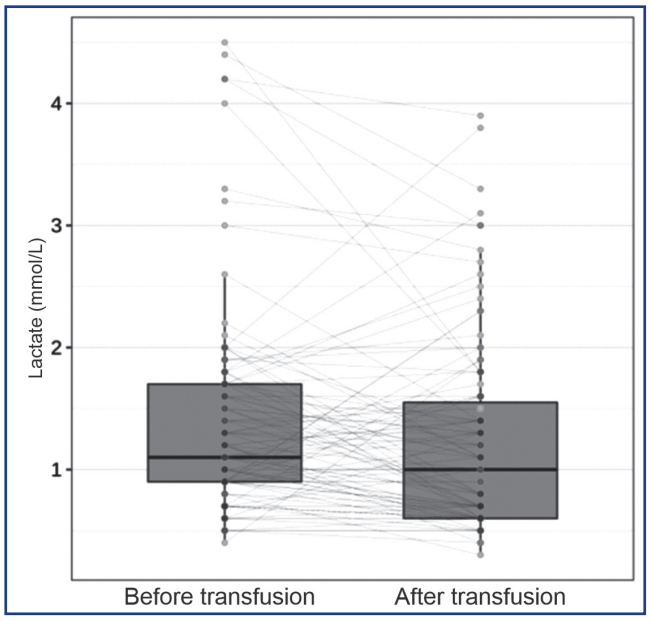

Figure 3 – Lactate levels before and after blood transfusion

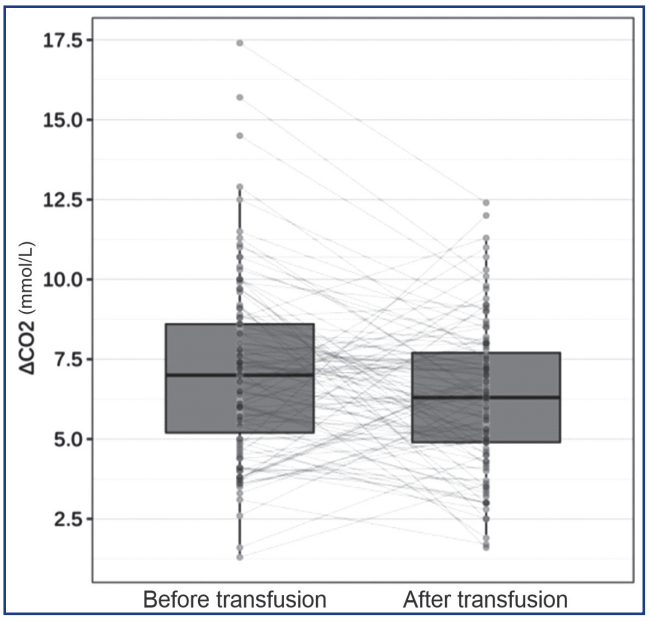

Figure 4 – ΔCO_2 levels before and after blood transfusion

Than, we analyzed the correlation between changes in the studied parameters and the initial level of oxygen extraction, which is the main indicator of oxygen delivery and consumption, and the initial level of hemoglobin, which is the main trigger for blood transfusion.

In the correlation analysis, a statistically significant correlation between the baseline oxygen extraction and the changes in blood transfusion was found in PvO_2 (ρ=0.39 (95% CI: 0.22; 0.54), p<0.001), lactate (ρ= -0.21 (95% CI: -0.39; -0.02), p=0.028) and ΔCO_2(ρ= -0.31 (95% CI: -0.47; -0.12), p=0.001) (Figures 5-7).

At that, no statistically significant correlation between the Hb baseline level and changes in response to blood transfusion was found in PvO_2 (ρ= -0.1 (95% CI: -0.28; 0.1), p=0.326) and ΔCO_2 (ρ=0.13 (95% CI: -0.07; 0.31), p=0.199) (Figures 8, 9). The lactate levels were statistically significantly and positively correlated with baseline Hb concentrations (ρ=0.35 (95% CI: 0.17; 0.51), p<0.001) (Figure 10).

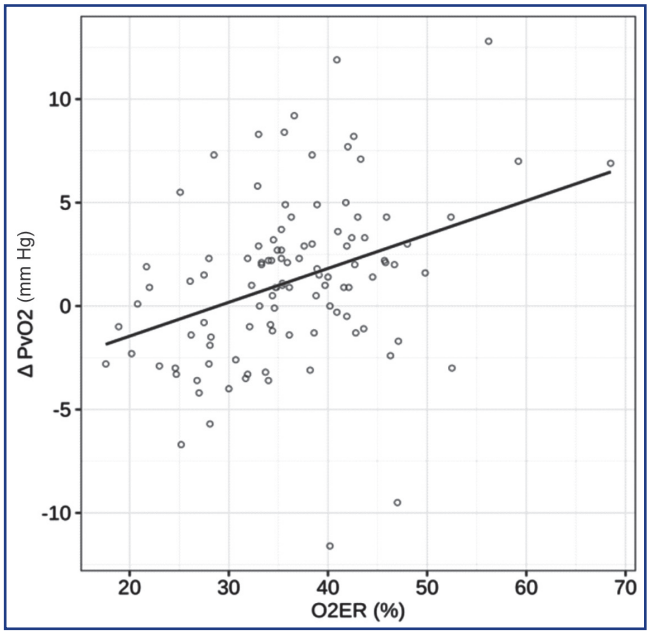

Figure 5 – Statistically significant correlation between changes of PvO2 in response to blood transfusion and O2ER baseline

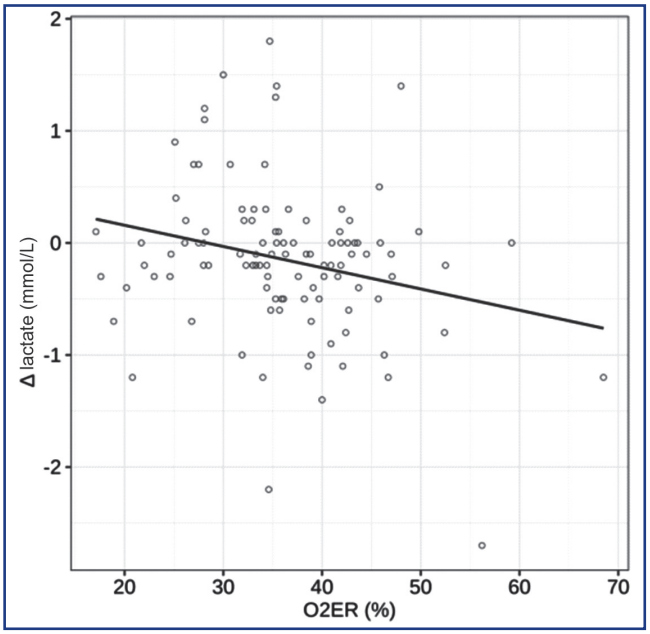

Figure 6 – Statistically significant correlation between lactate changes in response to blood transfusion and O2ER baseline

Further, the correlation between the level of O_2ER decline in response to transfusion of red blood cell components and the initial level of O_2ER, as well as between changes of O2ER and the concentration of Hb before blood transfusion, has been analyzed. The level of O_2ER decline (normalization) was statistically significantly correlat-

ed with the level of O_2ER before the intervention (ρ= -0.63 (95% CI: -0.73; -0.5), p<0.001): the higher the pre-transfusion of O_2ER level, the more significant was the level of normalization in response to transfusion of donor red blood cells. At the same time, there was no statistically significant association of O_2ER changes with baseline Hb concentration before surgery (ρ=0.16 (95% CI: -0.03; 0.34), p=0.105) (Figure 11).

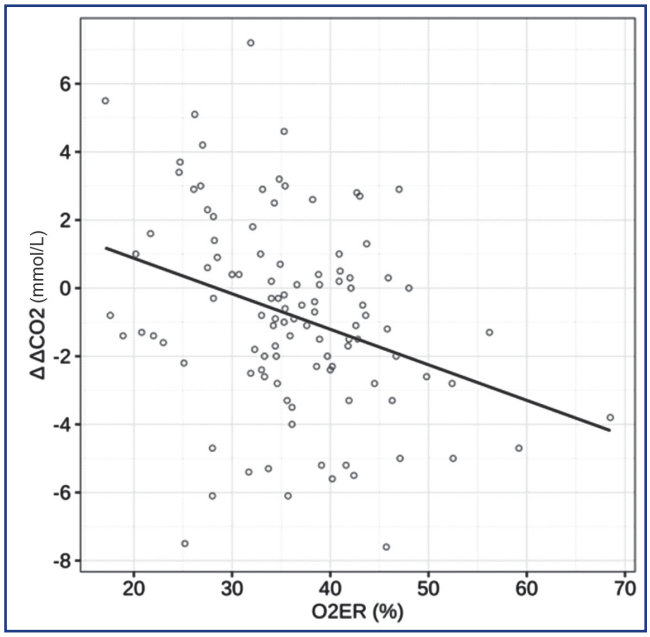

Figure 7 – Statistically significant correlation between changes in ΔCO_2 in response to blood transfusion and O_2ER baseline

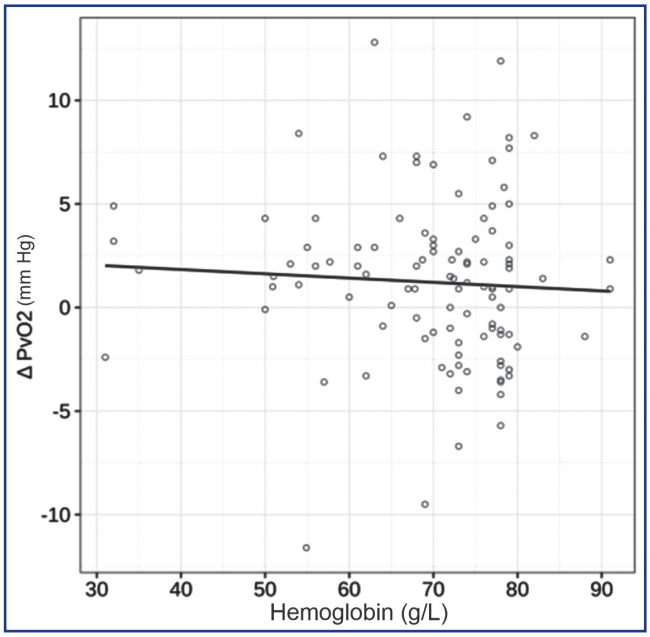

Figure 8 – No correlation between changes in PvO_2 in response to blood transfusion and baseline Hb levels

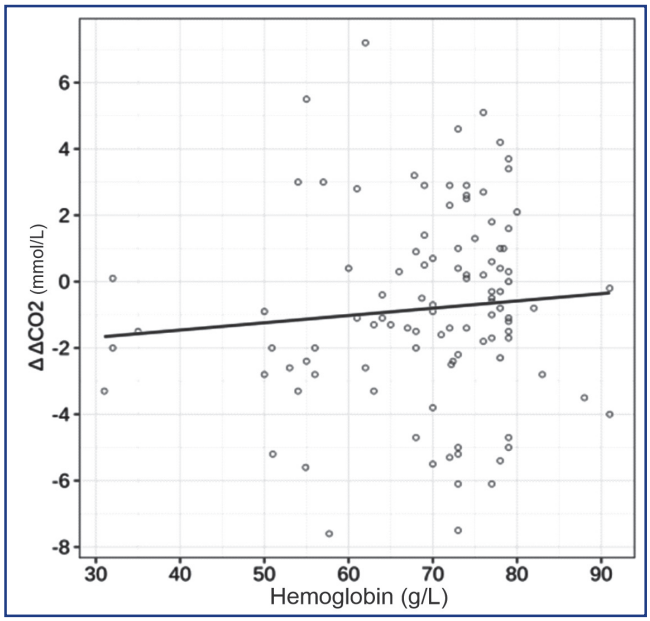

Figure 9 – No correlation between changes in ΔCO_2 in response to blood transfusion and baseline Hb levels

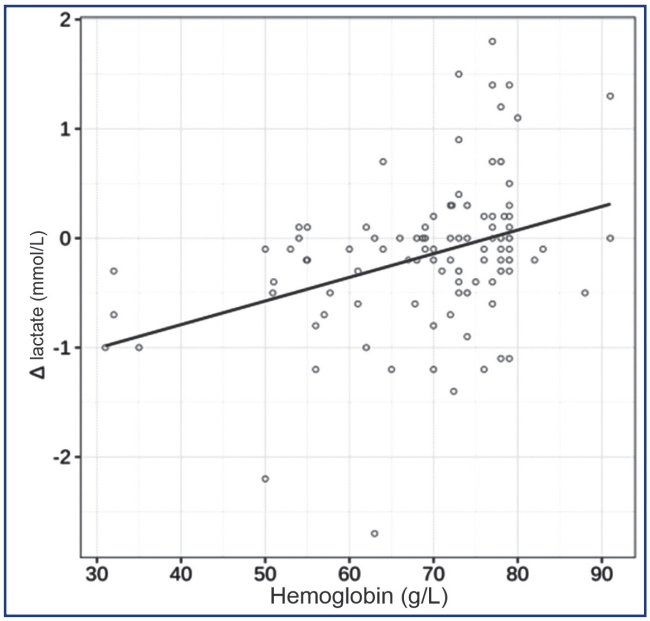

Figure 10 – Statistically significant correlation between changes in lactate levels in response to blood transfusion and baseline Hb levels

Discussion: Anemia is a multidisciplinary problem and is widespread in clinical practice. Both anemia and blood transfusion are associated with worsening clinical outcomes in different groups of patients [2,3,13-16]. However, the hemoglobin level does not reflect the true need for oxygen delivery in patients with anemia. This is especially critical in patients with concomitant cardiovascular pathology or acute cerebral insufficiency, and elderly patients. Our study demonstrated that the oxygen delivery indicators, such as PvO_2 and O_2ER, as well as tissue perfusion index ΔCO_2, were significantly changed towards normalization after the blood transfusion. Moreover, the worse the initial values of these parameters were, the more pronounced their normalization turned out to be found.

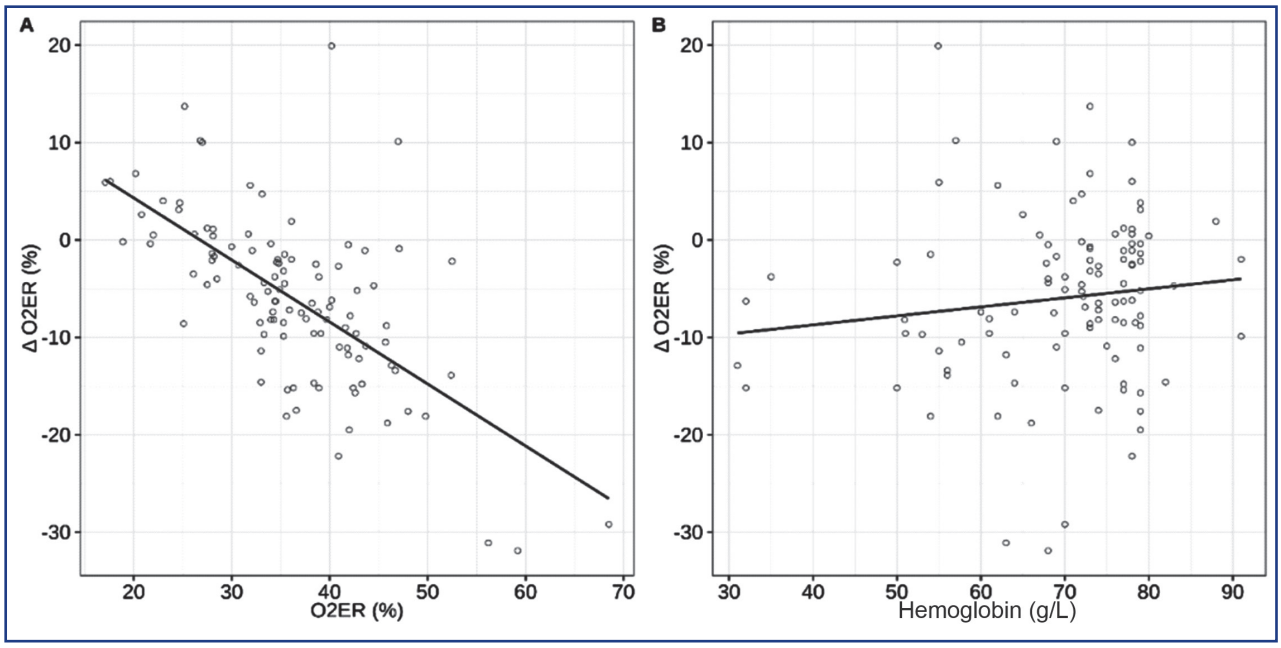

Figure 11 – Strong correlation between O2ER change in blood transfusion and baseline O2ER, no correlation between O2ER change and baseline Hb

The correlation analysis showed that all studied indicators, except for lactate, did not have a significant links with the initial level of hemoglobin. This indicates that the digital Hb index does not reflect the level of oxygen delivery and, accordingly, cannot serve as a reliable criterion for determination of the need for blood transfusion. The lactate levels showed a correlation with baseline Hb, however, their concentrations remained within the normal range both before and after the blood transfusion. The probable reason for this is the fact that the lactate levels respond to reduced oxygen delivery only when a critical threshold is reached, when compensatory mechanisms, such as increased cardiac output and tissue oxygen extraction, become inadequate [17]. Accordingly, in this clinical situation, the lactate cannot be considered as a trigger for blood transfusion. At the same time, changes in O_2ER, PvO_2 and ΔCO_2 indicate that these indicators can be used to make a decision on blood transfusion.

The results obtained are partially consistent with previously published studies. For example, B. Vallet in his studies showed the importance of using the central venous blood hemoglobin saturation as a trigger for blood transfusion [18, 19]. Another study conducted by Fogagnolo et al. demonstrated that the use of arteriovenous difference in oxygen content as a criterion for prescribing of blood transfusion leads to reduction of 90-day mortality in critically ill patients [20].

Our study has a number of limitations. First of all, it is not randomized, and blood transfusion was performed in all patients, which excludes the possibility of comparison with the control group. Secondly, critically ill patients, in whom the changes in oxygen delivery and consumption may be most pronounced, were excluded from the analysis.

Conclusion: Changes in O_2ER, PvO_2, and ΔCO_2 allow to consider these indicators as criteria for making a decision on blood transfusion. Currently, there is a growing interest in physiological and alternative triggers of transfusion, which is associated with the development of a personalized approach in transfusion practice and the desire to optimize the blood transfusion tactics in various categories of patients. Further research in this direction is needed, primarily to determine the threshold values of physiological triggers when prescribing the blood transfusion.

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АҢДАТПА

ОТТЕГІНІ ЭКСТРАКЦИЯЛАУ, ЛАКТАТ ДЕҢГЕЙІН, ОРТАЛЫҚ ВЕНОЗДЫҚ ҚАНДАҒЫ ОТТЕГІНІҢ ПАРЦИАЛДЫҚ ҚЫСЫМЫН ЖӘНЕ ВЕНОЗДЫ-АРТЕРИЯЛЫҚ КӨМІРҚЫШҚЫЛ ГАЗЫ АЙЫРМАШЫЛЫҒЫН ОНКОЛОГИЯЛЫҚ ПАЦИЕНТТЕРДЕ ГЕМОТРАНСФУЗИЯ КЕЗІНДЕ БАҒАЛАУ

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Өзектілігі: *Анемия – клиникалық практикада жиі кездесетін гематологиялық синдром, әсіресе онкологиялық пациенттер арасында оның жиілігі 40%-дан 90%-ға дейін жетеді. Анемияны туметудің негізгі әдісі қан құю (гемотрансфузия) болып табылады, алайда гемоглобин (Hb) деңгейі трансфузияны тағайындаудың жалғыз критерийі болып қала береді, бірақ ол әрдайым тіндердің оттегіге қажеттілігін дәл көрсете алмайды. Осыған байланысты соңғы жылдары O_2ER (оттегі экстракция коэффициенті), PvO_2 (орталық веноздық қанның оттегі парциалдық қысымы), Lac (лактат) және ΔCO_2 (веноздық-артериялық көмірқышқыл газы айырмашылығы) сияқты физиологиялық трансфузиялық триггерлер белсенді зерттелуде.*

Зерттеудің мақсаты: *Анемиясы бар онкологиялық пациенттерде гемотрансфузияның O_2ER, PvO_2, Lac және ΔCO_2 көрсеткіштеріне әсерін бағалау және оларды физиологиялық трансфузиялық триггерлер ретінде қолдану мүмкіндігін анықтау.*

Әдістер: *107 онкологиялық пациент қатысқан проспективті обсервациялық зерттеу жүргізілді. Гемотрансфузия алдында және одан 1 сағат өткен соң пациенттерден артериялық және орталық веноздық қан алынды, Hb, PvO_2, Lac, O_2ER*

және ΔCO_2 деңгейлері өлшенді. Статистикалық талдау Уилкоксон тесті және Спирмен рангілік корреляция коэффициенті көмегімен жүргізілді.

Нәтижелері: *Гемотрансфузиядан кейін негізгі көрсеткіштерде статистикалық тұрғыдан маңызды жақсару байқалды:*

- *O_2ER 35,4% (31,8; 41,9)-дан 29,3% (26,0; 33,4) дейін төмендеді ($p<0,001$);*
- *PvO_2 34,8 (32,7; 38)-ден 36 (34; 39) мм.сын.баг дейін артты ($p=0,005$);*
- *ΔCO_2 7 (5,2; 8,6)-дан 6,3 (4,9; 7,7) мм.сын.баг дейін төмендеді ($p=0,004$);*
- *Lac 1,1 (0,9; 1,7)-ден 1,0 (0,6; 1,55) ммоль/л дейін өзгерді ($p=0,005$), бірақ қалыпты шектерде қалды.*

Корреляциялық талдау нәтижесінде PvO_2, ΔCO_2 және Lac көрсеткіштері бастапқы O_2ER деңгейімен айтарлықтай байланысы анықталды, бірақ гемоглобиннің бастапқы деңгейімен корреляция байқалған жоқ ($p>0,05$). Бұл Hb деңгейі оттегіні жеткізу қажеттілігін дәл көрсетпейтінін, ал физиологиялық маркерлер трансфузияны тағайындаудың сенімдірек критерийлері болуы мүмкін екенін дәлелдейді.

Қорытынды: *Гемотрансфузиядан кейінгі O_2ER, PvO_2 және ΔCO_2 өзгерістері олардың физиологиялық трансфузиялық триггерлер ретінде қолданылу мүмкіндігін көрсетеді. Hb деңгейінен айырмашылығы, бұл параметрлер оттегімен қамтамасыз ету өзгерістерін дәлірек сипаттайды. Лактат Hb деңгейімен корреляцияланғанымен, оның деңгейі қалыпты диапазонда болғандықтан, оны сенімді трансфузиялық триггер ретінде қарастыру мүмкін емес. Болашақ зерттеулер физиологиялық трансфузиялық триггерлердің шекті мәндерін анықтау және олардың клиникалық нәтижелерге әсерін бағалау үшін қажет.*

Түйінді сөздер: *гемотрансфузия, анемия, оттегіні экстракциялау.*

АННОТАЦИЯ

ОЦЕНКА ЭКСТРАКЦИИ КИСЛОРОДА, УРОВНЯ ЛАКТАТА, ПАРЦИАЛЬНОГО ДАВЛЕНИЯ КИСЛОРОДА В ЦЕНТРАЛЬНОЙ ВЕНОЗНОЙ КРОВИ И ВЕНОАРТЕРИАЛЬНОЙ РАЗНИЦЫ ПО УГЛЕКИСЛОМУ ГАЗУ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ ПРИ ГЕМОТРАНСФУЗИИ

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Актуальность: *Анемия – распространенный гематологический синдромом, особенно среди онкологических пациентов. Гемотрансфузия остается основным методом коррекции анемии, однако единственным критерием для ее назначения служит уровень гемоглобина, который не всегда отражает доставку кислорода. В связи с этим изучаются альтернативные триггеры трансфузии: экстракция кислорода (O_2ER), парциальное давление кислорода в центральной венозной крови (PvO_2), уровень лактата (Lac) и веноартериальная разница по парциальному давлению углекислого газа ($\Delta CO2$).*

Цель исследования *– оценить влияние гемотрансфузии на O_2ER, PvO_2, Lac и ΔCO_2 у онкологических пациентов с анемией и определить возможное применение показателей в качестве физиологических триггеров трансфузии.*

Методы: *Проведено проспективное обсервационное исследование, включившее 107 онкологических пациентов с анемией, требующей гемотрансфузии. Всем пациентам выполняли забор артериальной и центральной венозной крови до и через 1 час после трансфузии. Оценивались концентрация гемоглобина (Hb), PvO_2, Lac, O_2ER и ΔCO_2. Для статистического анализа использовались критерий Уилкоксона и коэффициент ранговой корреляции Спирмена.*

Результаты: *После гемотрансфузии наблюдалось статистически значимое улучшение ключевых параметров:*

- *O_2ER снизился с 35,4% (31,8; 41,9) до 29,3% (26,0; 33,4) ($p<0,001$);*
- *PvO_2 увеличился с 34,8 (32,7; 38) до 36 (34; 39) мм рт. ст. ($p=0,005$);*
- *ΔCO_2 снизился с 7 (5,2; 8,6) до 6,3 (4,9; 7,7) мм рт. ст. ($p=0,004$);*
- *Lac изменился незначительно: 1,1 (0,9; 1,7) до 1,0 (0,6; 1,55) ммоль/л ($p=0,005$), оставаясь в норме.*

Анализ корреляций показал, что PvO_2, ΔCO_2 и Lac имели статистически значимую связь с исходным уровнем O_2ER, однако не коррелировали с базовым уровнем гемоглобина ($p>0,05$). Это подтверждает, что уровень Hb не отражает истинную потребность в доставке кислорода, а физиологические маркеры могут быть надежными критериями для назначения трансфузии.

Выводы: *Изменения O_2ER, PvO_2 и ΔCO_2 после гемотрансфузии позволяют рассматривать их в качестве триггеров трансфузии. В отличие от уровня гемоглобина, они точнее отражают снижения в доставке кислорода. Лактат не может быть надежным триггером трансфузии в данном исследовании, так как его уровень оставался в пределах нормы. Необходимы дальнейшие исследования в данном направлении.*

Ключевые слова: *гемотрансфузия, анемия, экстракция кислорода.*

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IMPROVING THE QUALIFICATIONS OF MEDICAL PERSONNEL AS A FACTOR FOR IMPROVING ONCOLOGICAL CARE IN KAZAKHSTAN

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ABSTRACT

Relevance: *The growing need for highly qualified medical personnel, especially in oncology, makes staff development essential in improving oncological care. The dynamically developing healthcare system of Kazakhstan requires adapting educational programs for medical professionals to modern requirements and challenges and ensuring their accessibility, regularity, and practical orientation.*

The study aimed to *analyze the effectiveness of professional development programs for medical personnel of the Kazakh Institute of Oncology and Radiology and their impact on the quality of oncological care.*

Methods: *The research utilized both quantitative and qualitative data collection methods. It included questioning employees of the Kazakh Institute of Oncology and Radiology medical institutions and analyzing statistical information.*

Results: *Key issues related to the accessibility and regularity of educational programs, staff's insufficient awareness of the possibilities of continuing education, and programs' inconsistency with current professional needs and the needs of medical professionals have been identified.*

Conclusion: *Increasing the effectiveness of professional development programs for medical personnel requires improving their accessibility, strengthening their practical orientation, and introducing modern training techniques. Implementing these recommendations will contribute to the growth of the professional level of medical workers, which, in turn, will improve the quality of oncological care in Kazakhstan.*

Keywords: *further training, medical staff, oncological care, education, Kazakhstan, innovation, professional development.*

Introduction: With the onset of the Fourth Industrial Revolution, accompanied by rapid changes in globalization, technological development, production, and social processes, the role and impact of lifelong learning on the development of individuals, organizations, and countries has increased significantly. In a knowledge-based and service-oriented economy, lifelong learning is critical to building an organization's human capital. An individual's knowledge and skills are a set of competencies. When they become an employee, their competencies turn into corporate human capital, so the management should support the lifelong learning of employees to contribute to the organization's development [1].

Investing in the development of human potential, the employer should develop and implement a human potential management system that will ensure continuous monitoring of key components, such as education and professional skills. International policy documents and standards confirm the need for such monitoring. This emphasizes the importance of skills analysis in the labor market and the educational sphere [2].

Training and professional development within lifelong learning are important drivers of change in the education system and business. This is the basis for improving the overall competitiveness of both employees and organizations as a whole. To support human development, it is crucial to create effective solutions to encourage and support lifelong learning, thus ensuring that employees are highly qualified at all stages of their professional lives [3].

In line with the measurements and management actions taken, outcomes related to workforce development, understanding, acceptance, alignment with strategic objectives, continuous learning, and evaluation should be expected. As the fifth dimension emphasizes, it is crucial to implement evaluation and control systems to monitor the contribution of employees' qualifications [4].

In critical areas such as health care, workforce management can be essential not only to ensure productivity, profitability, and competitiveness. Monitoring the skills of the health workforce can also improve the quality of care and patient safety. The healthcare workforce can be defined as people involved in activities that aim to promote health. This definition includes clinical, managerial, and support workers [5].

The Organization for Economic Cooperation and Development (OECD) Adult Skills Survey indicates a sig-

nificantly higher level of skills mismatch among health workers than other professional workers, indicating the risk of a skills gap. Skills mismatch can be caused by deficiencies in education and training systems, as well as deficiencies in health systems and workplace organization, so a systematic approach to skills assessment is needed. In addition, it is vital for health workers not only to have the necessary skills but also to use them effectively [6].

As recommended by the World Health Organization (WHO), transformative, high-quality education and lifelong learning must be implemented to ensure that all health workers have skills relevant to the health needs of the population and can perform to their full potential; education and training must be practice-oriented and tailored to the needs of the health system. Thus, effective and purposeful human capital management can serve not only personal growth and the strategic goals of healthcare organizations but also the functioning of the public health system [7, 8].

The study aimed to analyze the effectiveness of professional development programs for medical personnel of the Kazakh Institute of Oncology and Radiology (KazIOR) and their impact on the quality of oncological care.

Materials and methods: The target group of the study consisted of 100 employees (including medical workers and support staff) of KazIOR. The probability sampling method was used to select respondents. Each of the study participants voluntarily agreed to participate in the questionnaire.

The study assesses employee satisfaction with existing educational programs, identifies barriers and problems that prevent effective training, and develops recommendations to improve the system of continuing professional education of health workers. The study assessing the effectiveness of continuing professional development programs at KazIOR was conducted using a combined methodology, including quantitative and qualitative data collection methods. The primary information collected from the organization's employees was quantitative. For this purpose, a questionnaire including closed-ended questions based on the Likert scale was developed. The questionnaire was pre-tested to ensure clarity of questions and to obtain reliable and accurate data. The questions in the questionnaire covered various aspects related to professional development programs, such as relevance, usefulness, frequency of participation, and employee satisfaction.

Survey: To improve staff qualification, the Center regularly organizes various workshops and training, among which are: "Modern Methods of Diagnosis and Treatment of Malignant Tumors" (120 hours), "General Nursing Technologies" (120 hours), "Innovative Technologies in Laboratory Diagnostics" (120 hours), "Management in Nursing" (120 hours), "Resuscitation and Intensive Care in Emergency Conditions" (120 hours) and "Nursing Competencies in Oncology" (120 hours). In addition to these courses, the Center also conducts other educational programs to improve health workers' professional skills. These activities contribute to improving the competence of specialists, sharing experience among staff, and introducing modern approaches into clinical practice.

We offered open-ended questions To better understand employees' needs and preferences and collect the participants' opinions on possible improvements to the educational programs. The questionnaire was carefully designed to gather information from KazIOR employees on possible key variables that clarify the selection criteria used to allocate funding to employees and identify the benefits associated with the fact that funding improves employee productivity and the organization's sustainability potential. The questions covered topics such as relevance and usefulness of training, frequency of participation, employee satisfaction, and evaluation of workshops and courses conducted at KazIOR. The questionnaire allowed for assessing the relevance and demand for such training among the staff. To determine and ensure the validity of the questionnaire, it was pre-tested, considering the sample size to ensure a thorough comparison of the research questions and objectives and to create an effective and reliable data collection tool.

Data Analysis: The primary data collected from the respondents were coded in the SPSS software (version 23.0). The collected data were cross-checked to ensure that there were no errors. A chi-square test was conducted to analyze the relationship of the variables. Cronbach's alpha test with a significance coefficient of 0.75 was used to test the reliability and validity of this study. The overall reliability scores below were high (0.908) for the six items tested. This indicates a high degree of acceptability and consistency of scores across categories in this study. Data analysis revealed key aspects that influence the effectiveness of professional development programs and employee satisfaction.

Results: In the course of the study aimed at assessing the satisfaction of the medical staff of KazIOR with professional development programs, 100 institution employees were interviewed. Respondents assessed professional development programs' relevance, usefulness, and impact on their professional activities. The study results are statistical data based on a five-point

Likert scale. For each statement, a Chi-square test was conducted.

1. *Relevance of professional development programs:* When asked how relevant professional development programs are to providing oncological care, as seen in Figure 1, 72% of respondents rated them as relevant or very relevant. Specifically, 42% of respondents rated them as "5" (very relevant) and 30% rated them as "4" (mostly relevant). Meanwhile, 18% of respondents expressed a neutral attitude (rated "3"), and 10% found the programs to be marginally relevant (rated "2").

The results of the Chi-square test of goodness of fit showed that this result was statistically significant (standard value = 1.5897; mean = 4.12; p=0.000).

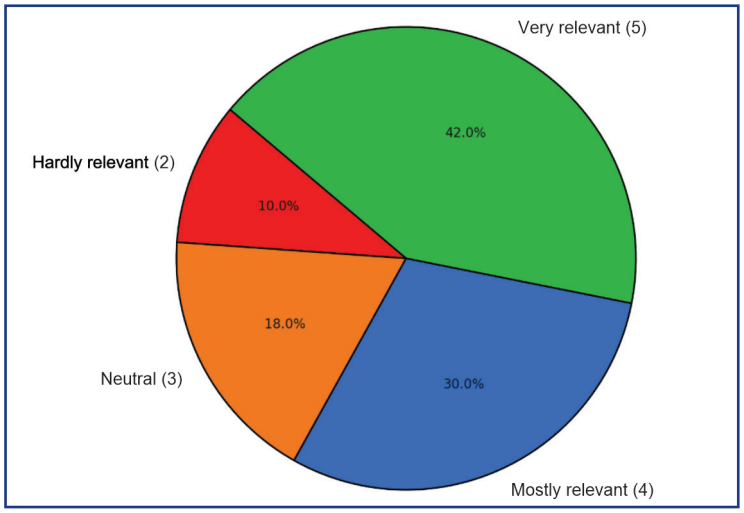

Figure 1 – Relevance of professional development programs conducted at KazIOR

2. *Satisfaction with professional development opportunities:* On the question of satisfaction with current professional development opportunities, 60% of respondents expressed satisfaction by rating "4" (satisfied), and 18% were fully satisfied (rating "5"). At the same time, 15% of respondents reported partial dissatisfaction (rated "2") and 7% were completely dissatisfied (rated "1") (Figure 2).

The results of the Chi-square test of goodness of fit showed that this result was statistically significant (standard value = 1.3456; mean = 3.84; p=0.000).

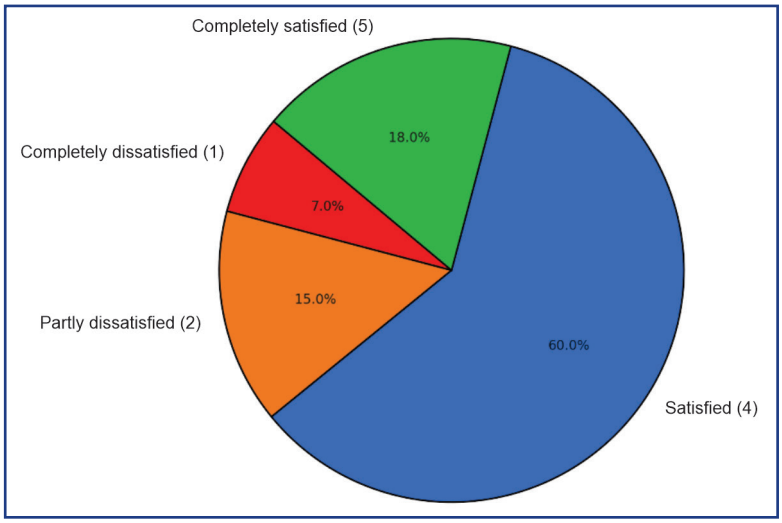

Figure 2 – Employee satisfaction with professional development opportunities provided at KazIOR

3. *Usefulness of professional development courses:* An assessment of the courses' usefulness in improving the quality of cancer care for patients showed that 70% of respondents found them useful or very useful. 40% of participants rated them at "5" and 30% at "4". 16% of respondents gave a neutral rating ("3"), and 14% found the courses to be not useful or not very useful (scores "1" and "2") (Figure 3).

The results of the Chi-square test of goodness of fit showed that this result was statistically significant (standard value = 1.4502; mean = 4.01; p=0.000).

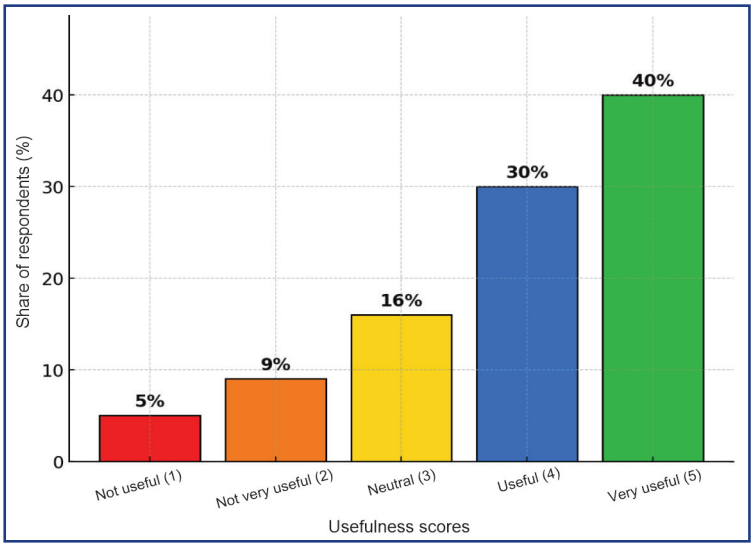

Figure 3 – Usefulness of professional development courses by the assessment of KazIOR employees

4. *Frequency of participation in training and workshops:* The illustration in Figure 4 shows that the frequency of opportunities to participate in training, workshops and professional development courses was quite high: 58% of respondents stated that such events are held regularly (rated "5"), and 25% stated that they are held frequently (rated "4"). Only 13% of respondents indicated that they rarely participate in such events (rated "2"), and 4% do not participate in them at all (rated "1").

The results of the Chi-square test showed that this result was statistically significant (standard value = 1.6821; mean = 4.10; p=0.000).

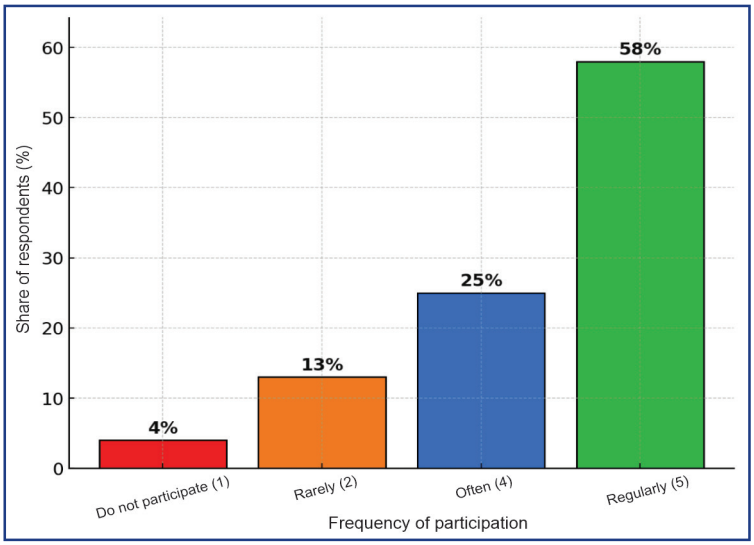

Figure 4 – Frequency of participation in training and workshops of KazIOR employees

5. *Quality of professional development courses:* As shown in Figure 5, according to most respondents, the qualifications and skills of trainers of professional development courses are satisfactory overall. 47% of the respondents rated it as "4" (high level), and 30% rated it as "5" (very high level). However, 18% of the employees shared doubts about the quality of teaching, rating it as "2", and 5% gave the lowest rating of "1".

The results of the Chi-square test showed that this result was statistically significant (standard value = 1.3025; mean = 3.85; p=0.000).

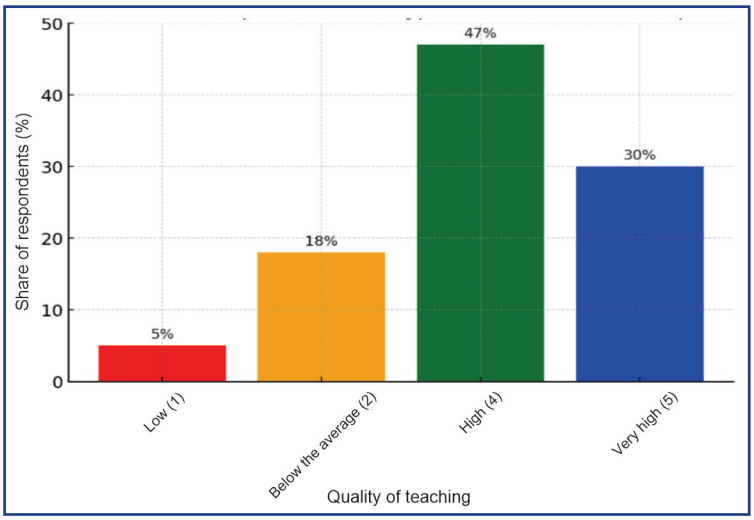

Figure 5 – Quality of professional development courses provided at KazIOR

6. *Impact of professional development on excelling qualification:* Regarding the impact of professional development courses on professional growth and efficiency in working with patients, as can be seen in Figure 6, 60% of respondents indicated that the training significantly improved their professional skills and increased their efficiency (rating "5"). 25% believe that the training has brought some improvements (rating "4"), and 10% did not notice any changes in their work after taking the courses (rating "3").

The results of the Chi-square test showed that this result was statistically significant (standard value = 1.5783; mean = 4.12; p=0.000).

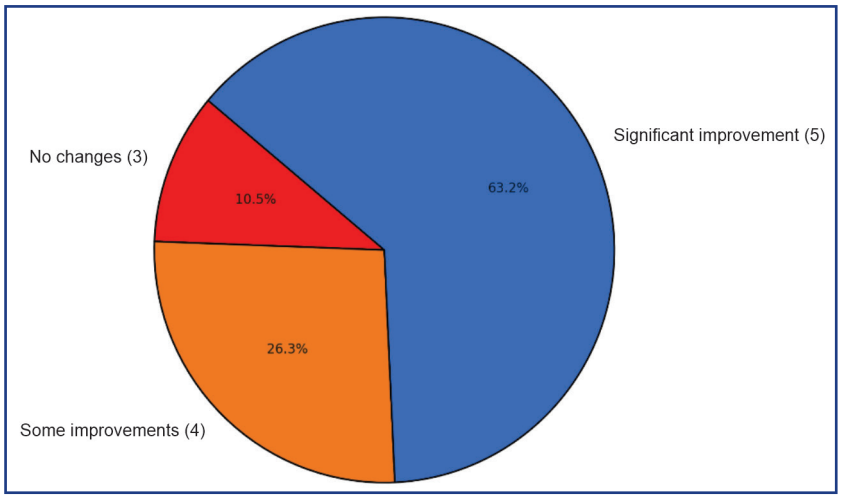

Figure 6 – Impact of professional development on excelling qualification of the employees of KazIOR

7. *Needs for improvement of the professional development system:* According to the open-ended questions of the questionnaire, the majority of respondents expressed a desire to improve the professional development system, suggesting an increase in the frequency of courses in specific areas of oncology, as well as an increase in the practical component of training. Some respondents also indicated the need to improve the quality of educational materials and the training format, for example, by using modern technologies.

Recommendations: Based on the study results, we can identify several key recommendations aimed at improving the system of professional development of KazIOR employees.

First, it is important to periodically update the content of continuing education programs to reflect the latest advances in oncology. This will help ensure that the courses are up-to-date and aligned with modern medical standards. Regular updates will keep staff up-to-date with new diagnostic and

treatment methods, directly impacting patient care quality.

In addition, to make educational programs available to more staff, additional courses and training should be organized regularly. This will ensure that all professionals, regardless of their work schedule, have the opportunity to receive training and professional development. Such changes will ensure that all employees are reached, ensuring that they have the opportunity to grow professionally and improve their skills.

It is also worth paying attention to improving the practical component of the courses. Training programs must include more practical exercises, training, and case studies. This will help staff apply their knowledge in practice and improve their work with patients, improving the quality of cancer care.

In addition, to improve the effectiveness of educational programs, it is necessary to invest in the professional training of teachers. Improving pedagogical skills and continually updating faculty members' knowledge of oncology will allow for the creation of better and more relevant courses. It is also important to establish a system of regular feedback from course participants, which will allow timely identification of shortcomings in the educational process and adjustment of teaching approaches.

An equally important aspect is the integration of modern technologies into the training process. Using online courses, virtual simulators, and tools will make education more accessible, especially for those employees who cannot attend training due to busy work schedules or locations. This will provide flexibility and convenience in the professional development process.

In addition, there is a need to develop a system that will track the impact of courses on employees' professional skills. With such a system, it will be possible to identify which courses have the greatest impact on improving the quality of work and which courses need to be refined. This will allow efforts to be directed towards further improvement of educational programs, making them as effective as possible.

Another important aspect is to ensure that training is individualized. Different levels of employees' knowledge and needs should be considered when organizing courses. Providing a choice of courses depending on professional specialization and skill level will allow each employee to develop the skills needed for their job, ultimately improving the team's overall performance.

Finally, attention should be paid to expanding the range of specialized courses. Including new programs related to specific areas of oncology, such as innovative diagnostics, treatment and palliative care methods, will help staff deepen their knowledge and improve their skills in specific areas. This will also positively impact the quality of cancer care and the development of the specialists.

Discussion: The study's results confirm that professional development programs conducted in KazIOR play a key role in improving oncological care. The high level of employee satisfaction indicates the demand for educational activities. However, barriers related to the lack of staff awareness of training opportunities and inconsistent program content with current professional demands were identified. This indicates the need to modernize the continuing medical education system, introduce more flexible and practice-oriented training methods, and strengthen information support. Improving the availability and quality of educational initiatives in KazIOR can contribute to the growth of the professional competence of medical workers and, as a consequence, increase the efficiency of oncologic care.

Conclusion: The KazIOR staff development program aims to develop employees' professional skills by creating opportunities for their training and improvement. This allows for maintaining a high level of employee qualification and contributes to improving medical services in oncology, which is important for the organization's sustainability and growth. The program aims to develop each employee's potential, ultimately improving the team's overall performance.

The findings of our study show that, despite the availability of the professional development program, it does not fully fulfill its task and has no proper impact on improving employees' professional skills. The main obstacles are the limited availability of educational programs and a lack of information about this program's opportunities. This has resulted in most employees not seeing significant improvement in their professional performance and believing there is no tangible benefit from participating in the program. Thus, a lack of awareness and unclear communication about the program's purpose and benefits made it less effective.

In addition, the study found that a lack of regular and systematic professional development programs reduces an organization's flexibility and ability to adapt quickly to new demands in the field of oncology. Continuing education programs must be regularly reviewed to keep pace with changes in medical standards and new technological advancements, ensuring that employees are always one step ahead in their professional activities. Thus, regularly updating educational programs is key to the organization's success.

Also, the study's results emphasize that insufficient evaluation of the effectiveness of educational courses

leads to insufficient adaptation of programs to the real needs of employees and the organization. The introduction of mechanisms for monitoring and regular evaluation of the effectiveness of programs will allow for a more accurate assessment of their relevance and feasibility, as well as timely adjustments. This will ensure higher efficiency and allow the organization's resources to be used effectively.

The study's findings confirm that an employee development program is important for developing individual professionals and the organization. However, for the program to impact skills development and productivity, significant improvements are needed in its accessibility, employee awareness, and the regularity of the courses. Having all stakeholders understand the program's benefits and clearly define its objectives will ensure educational initiatives' success and long-term effectiveness.

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АҢДАТПА

ҚАЗАҚСТАНДА ОНКОЛОГИЯЛЫҚ КӨМЕКТІ ЖЕТІЛДІРУ ФАКТОРЫ РЕТІНДЕ МЕДИЦИНАЛЫҚ ПЕРСОНАЛДЫҢ БІЛІКТІЛІГІН АРТТЫРУ

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Өзектілігі: *Жоғары білікті медициналық кадрларға, әсіресе онкология саласында өсіп келе жатқан қажеттілік персоналдың біліктілігін арттыруды онкологиялық көмекті жетілдірудің маңызды факторына айналдырады. Қазақстанның қарқынды дамып келе жатқан денсаулық сақтау жағдайында медицина қызметкерлеріне арналған білім беру бағдарламаларын олардың қолжетімділігін, жүйелілігін және практикалық бағыттылығын қамтамасыз ете отырып, қазіргі заманғы талаптар мен сын-тегеуріндерге бейімдеу қажет.*

Зерттеудің мақсаты *– "Қазақ онкология және радиология ғылыми-зерттеу институты" АҚ медициналық персоналының біліктілігін арттыру бағдарламаларының тиімділігін және олардың онкологиялық көмектің сапасына әсерін талдау.*

Әдістері: *Зерттеу деректерді жинаудың сандық және сапалық әдістерін қолдануды қамтиды. Жұмыс барысында "Қазақ онкология және радиология ғылыми-зерттеу институты" АҚ қызметкерлеріне сауалнама жүргізу, статистикалық ақпаратты талдау, сондай-ақ кәсіптік даярлық талаптарына сәйкестігін тестілеу қолданылды.*

Нәтижелері: *Білім беру бағдарламаларының қолжетімділігі мен жүйелілігіне, қызметкерлердің білім беруді жалғастыру мүмкіндіктері туралы хабардар болмауына, сондай-ақ бағдарламалардың медицина қызметкерлерінің өзекті кәсіби сұраныстары мен қажеттіліктеріне сәйкес келмеуіне қатысты негізгі проблемалар анықталды.*

Қорытынды: *Медициналық персоналдың біліктілігін арттыру бағдарламаларының тиімділігін арттыру үшін олардың қолжетімділігін жақсарту, практикалық бағыттылығын күшейту және оқытудың заманауи технологияларын енгізу қажет. Осы ұсынымдарды іске асыру медицина қызметкерлерінің кәсіби деңгейінің өсуіне ықпал етеді, бұл өз кезегінде Қазақстанда онкологиялық көмектің сапасын жақсартуға әкеледі.*

Түйінді сөздер: *біліктілікті арттыру, медициналық персонал, онкологиялық көмек, білім беру, Қазақстан, инновация, кәсіби даму.*

АННОТАЦИЯ

ПОВЫШЕНИЕ КВАЛИФИКАЦИИ МЕДИЦИНСКОГО ПЕРСОНАЛА КАК ФАКТОР СОВЕРШЕНСТВОВАНИЯ ОНКОЛОГИЧЕСКОЙ ПОМОЩИ В КАЗАХСТАНЕ

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Актуальность: *Растущая потребность в высококвалифицированных медицинских кадрах, особенно в сфере онкологии, делает повышение квалификации персонала важнейшим фактором совершенствования онкологической помощи. В условиях динамично развивающегося здравоохранения Казахстана необходимо адаптировать образовательные программы для медицинских работников к современным требованиям и вызовам, обеспечивая их доступность, регулярность и практическую направленность.*

Цель исследования *– анализ эффективности программ повышения квалификации медицинского персонала АО «Казахский научно-исследовательский институт онкологии и радиологии» (КазНИИОиР, Алматы, Казахстан) и их влияния на качество онкологической помощи.*

Методы: *Исследование включает использование как количественных, так и качественных методов сбора данных. В ходе работы применялись анкетирование сотрудников АО «Казахский научно-исследовательский институт онкологии и радиологии», анализ статистической информации.*

Результаты: *Выявлены ключевые проблемы, касающиеся доступности и регулярности программ повышения квалификации, недостаточной осведомленности сотрудников о возможностях продолжения образования, а также несоответствия программ актуальным профессиональным запросам и потребностям медицинских работников.*

Заключение: *Для повышения эффективности программ повышения квалификации медицинского персонала необходимо улучшение их доступности, усиление практической направленности и внедрение современных технологий обучения. Реализация данных рекомендаций будет способствовать росту профессионального уровня медицинских работников, что, в свою очередь, приведет к улучшению качества онкологической помощи в Казахстане.*

Ключевые слова: *повышение квалификации, медицинский персонал, онкологическая помощь, образование, Казахстан, инновации, профессиональное развитие.*

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DYNAMIC ASSESSMENT OF QUALITY OF LIFE ASSOCIATED WITH VISUAL IMPAIRMENT IN PATIENTS RECEIVING CHEMOTHERAPY

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ABSTRACT

Relevance: *Chemotherapy and targeted therapy used in cancer treatment are often associated with side effects that affect visual function. Such complications include dry eye syndrome, cataracts, keratopathy, and retinopathy, which can significantly worsen patients' quality of life. This work focuses on assessing the quality of life of cancer patients experiencing visual impairment and the importance of monitoring these side effects.*

The study aimed to *explore the quality of life of cancer patients with visual impairments resulting from exposure to chemotherapy and targeted therapy, with special attention to the timing of visual complications, their severity, and reversibility.*

Methods: *The study analyzed 65 scientific articles in Russian and English published in PubMed, Embase, Cochrane Library, Scopus, Web of Science, and Google Scholar databases from 2012 to 2024. The search used keywords related to chemotherapy, toxic effects on vision, and malignant neoplasms. The study included meta-analyses, systematic reviews, controlled clinical trials, and individual case reports.*

Results: *Chemotherapeutic drugs such as cisplatin and paclitaxel cause visual impairment, including dry eye syndrome, red eyes, cataracts, and retinopathy. Targeted drugs such as bevacizumab and erlotinib cause corneal damage, conjunctivitis, and uveitis. Visual impairment significantly worsens patients' quality of life, creating difficulties in performing everyday tasks such as reading, driving, and recognizing faces. These impairments also cause discomfort, dry eyes, and lacrimation and can lead to decreased visual acuity. In rare cases, the consequences of such impairments lead to partial or complete loss of vision, which seriously affects the patient's social functioning and emotional state. The use of special ophthalmological questionnaires allows for the early detection of side effects, which helps improve patients' quality of life.*

Conclusion: *Dynamic quality of life assessment represents a promising approach to understanding and addressing visual impairment in patients receiving chemotherapy and targeted therapy. These methods consider temporal variations and contextual factors that influence quality of life, opening the way for personalized interventions that may improve treatment outcomes.*

Keywords: *chemotherapy, targeted therapy, visual impairments, quality of life.*

Introduction: The International Agency for Research on Cancer (IARC) has estimated that there will be 20 million new cases of cancer and 9.7 million cancer-related deaths in 2022 [1]. Among the most frequently diagnosed cancers, lung cancer and breast cancer stand out, accounting for 2.5 million and about 2.3 million new cases, respectively [2].

Lung cancer was the most common cancer worldwide in 2022, accounting for 12.4% of all cancer cases, or every eighth diagnosis. Breast cancer among women is in second place with a share of 11.6% [3], followed by colon cancer (9.6%), prostate cancer (7.3%) and stomach cancer (4.9%) [1, 4].

According to GLOBOCAN forecasts, by 2050, the number of new cancer cases could reach 35 million annually. This creates a serious need for significant investments in the prevention, early diagnosis, and treatment of cancer diseases [1].

Oncological diseases in Kazakhstan rank 7th among all diseases and 2nd in mortality after circulatory diseases. Today, more than 205 thousand patients with cancer are registered, and over 37 thousand new cases are registered annually. The incidence among women is higher than among men (57% versus 43%) [5]. This is explained by the fact that breast cancer ranks first in the morbidity structure [6, 7]. Of those affected, 56% are working-age [8, 9].

Modern treatment methods have significantly increased patient survival in recent decades [10, 11]. However, methods such as chemotherapy and targeted therapy are associated with several systemic and ocular side effects that can seriously affect the patients' quality of life [12]. Mild or severe visual impairment can significantly hinder the performance of daily tasks and decrease the quality of life [13]. Therefore, careful monitoring and treatment of such complications by an ophthalmologist is necessary, especially in patients with pre-existing eye disease.

Chemotherapy and targeted therapy are associated with side effects such as photophobia, cataract, glaucoma, and retinopathy [14]. Some targeted drugs cause specific ocular side effects: imatinib can cause periorbital edema and epiphora, cetuximab can cause corneal damage and blepharitis, erlotinib can cause ocular

surface problems, and bevacizumab can cause thromboembolic complications [15, 16]. These effects develop due to cytotoxicity, inflammation, and neurotoxicity [17].

Thus, the study of dynamic assessment of the quality of life of patients who have visual impairment as a result of chemotherapy is relevant for increasing the effectiveness of complex therapy and improving the quality of life of patients. Including a dynamic assessment of visual functions in the general treatment of cancer will allow for the prediction of the consequences of chemotherapy and improve treatment planning by considering visual impairment. This, in turn, will help to ensure a more personalized approach to treatment, minimizing negative side effects and improving patients' quality of life.

The study aimed to explore the quality of life of cancer patients with visual impairments resulting from exposure to chemotherapy and targeted therapy, with special attention to the timing of visual complications, their severity, and reversibility.

Materials and methods: A structured literature search was conducted in the PubMed, Embase, Cochrane Library, Scopus, Web of Science, and Google Scholar databases using a combination of Medical Subject Headings (MeSH) and keywords related to chemotherapy, targeted therapy, visual impairment, and quality of life in patients with cancer. Key search terms included chemotherapy, targeted therapy, visual impairment, uveitis, retinopathy, quality of life, cancer treatment, side effects, and cancer patients. Studies published between January 2012 and December 2024 were considered to ensure data relevance. Inclusion criteria included meta-analyses, controlled and original studies, cross-sectional studies, systematic reviews, and case reports. Articles that did not have an evidence base were excluded. A total of 65 sources met the inclusion criteria. The search included peer-reviewed articles in English and Russian.

Results: Chemotherapy and targeted therapy drugs significantly impact the visual organ, causing direct and indirect cytotoxic effects.

Direct cytotoxic effects include damage to ocular structures such as the conjunctiva, cornea, retina, and optic nerve with local and systemic administration of drugs. G. Wang et al. claim that methotrexate causes apoptosis in retinal cells, contributing to the development of retinopathy and neuropathy [18]. I. Ferah Okkay et al. found that alkylating agents such as cisplatin induce DNA damage and oxidative stress, which is clinically manifested by conjunctivitis, keratopathy, and uveitis [19]. Chemotherapy used in the treatment of malignant neoplasms can cause various complications in the visual organs. A study involving patients with brain gliomas receiving intra-arterial chemotherapy revealed the following ocular complications: retinal angiospasm was observed in 21.8% of patients, retrobulbar neuritis was noted in 12.7% of patients, neuroretinitis was detected in 10.9% of patients. In addition, decreased visual acuity was recorded in 25.5% of patients, absolute central scotoma in 12.7%, relative central scotoma in 14.5%, and concentric narrowing of the peripheral visual field in 7.3% of patients [20].

Indirect cytotoxic effects are associated with systemic toxicity of drugs, leading to inflammation and oxidative stress of the whole organism [21]. For example, 5-fluorouracil stimulates the production of proinflammatory cytokines (IL-6, TNF-α), which worsens the stability of the tear film and causes dry eye syndrome [22]. According to F. Canino et al., systemic inflammation and vascular dysfunction can impair the microcirculation of the eye, contributing to ischemia of the vessels of the eyeball and can further lead to retinopathy and optic neuropathy [23]. Understanding these mechanisms is of key importance for preventing and treating ocular complications in cancer patients, which helps improve their quality of life and vision.

Research into the ocular side effects of chemotherapy and targeted therapy focuses on identifying toxic effects on the eye, their impact on patients' quality of life, and developing assessment methods and treatment approaches.

Table 1 – Impact of ophthalmological side effects on quality of life during chemotherapy and targeted therapy

Characteristic	Chemotherapy	Targeted therapy
Toxic effects on the organ of vision	Dry eye syndrome, red eye, foreign body sensation, cataract, retinopathy, macular hole, optic neuropathy	Dry eye syndrome, conjunctivitis, uveitis, corneal changes, lower eyelid eversion
Ophthalmic impact on quality of life	Difficulty reading, driving, recognizing faces, discomfort, dry eye, decreased vision, vision loss	Difficulty reading, driving, recognizing faces, tearing, discomfort
Intervention measures	Treatment of the cornea and conjunctiva, regular vision, and fundus examinations. Collaboration between oncologists, ophthalmologists, and psychologists for a comprehensive approach to treatment	Treatment of the cornea and conjunctiva, regular vision examinations. Collaboration between oncologists, ophthalmologists, and psychologists for a comprehensive approach to treatment

Visual disturbances associated with chemotherapy and targeted therapy.

Chemotherapeutic drugs cause complications, including dry eye syndrome [20, 24], keratopathy [25], cataracts, retinopathy, optic neuropathy [26, 27], and macular holes [28, 29] (Tables 1 and 2).

Carboplatin is considered less ocular toxic than its analog cisplatin, but it can still cause ophthalmological side

effects, especially at high doses or for long periods [30]. In contrast, cisplatin has greater toxicity to the retina and optic nerve, which can lead to the development of serious complications such as optic neuropathy or ischemic retinopathy. For example, S. Shihadeh et al. described a clinical case of a patient with neuroendocrine bladder cancer who developed rapidly progressive bilateral optic neuropathy during treatment with cisplatin. Despite the use of high doses of steroids, the patient's condition did not improve, which emphasizes the severity of this complication [30]. A similar case was described in a 16-year-old patient receiving cisplatin for the treatment of Hodgkin's lymphoma. The patient developed toxic optic neuropathy, which led to significant vision loss. This case highlights the potential risk of ophthalmologic complications with cisplatin, especially in young patients, and the need for careful monitoring of the optic nerve during therapy [26]. A study by J. Kim et al. described a case of a 79-year-old man with small-cell lung cancer who developed irreversible bilateral vision loss after polychemotherapy with carboplatin and cisplatin. Examination revealed retinal artery stenosis, diffuse thinning of choroidal and retinal tissues, and retinal vascular ischemia. Polychemotherapy can lead to irreversible vision loss, which highlights the importance of physicians being aware of the potential ocular toxicity of these drugs [31].

Table 2 – Chemotherapeutic drugs and their toxic effects on the visual organ

Preparations	Indications for use	Clinical manifestations	An object of toxic action	Notes
Cisplatin	Cisplatin is used in the treatment of various malignant tumors.	Retrobulbar neuropathy, optic neuritis, color blindness, central blindness, homonymous hemianopsia, retinopathy, retinal vascular occlusion	Optic nerve and retina	Discontinuation of cisplatin treatment results in improvement of the condition
Carboplatin	Carboplatin is used to treat various malignant tumors but with better tolerability.	Blurred vision, changes in color perception, metamorphopsia, dry eye syndrome. Optic neuropathy (rare)	Cornea	It is recommended to monitor vision when carboplatin is prescribed, especially with long-term use.
Taxan	Drugs such as paclitaxel and docetaxel are used to treat breast, lung, and ovarian cancers.	Dry eye syndrome, cystoid macular edema, diplopia, eyelash alopecia, blepharitis, meibomian gland dysfunction, tubular obstruction	Lacrimal glands, cornea, meibomian glands, retina	If necessary, replacement with other drugs is possible.
Antimetabolites	Methotrexate and 5-fluorouracil are widely used in the treatment of various malignant tumors.	Corneal xerosis, lacrimal duct obstruction, punctate epithelial keratopathy, conjunctival hyperemia, blepharitis	Corneal epithelium, lacrimal duct obstruction, lacrimal drainage dysfunction	Regular ophthalmological examinations and treatment of lacrimal duct obstruction, prevention of xerosis

In a study by E. Cosmo et al., changes in the cornea in patients with breast cancer treated with paclitaxel were studied using confocal microscopy. The changes revealed resulted in eye discomfort and lacrimation, significantly reducing the patients' quality of life. The method made it possible to detect early changes in the corneal layers [24].

A similar study by JCB Chiang et al. confirmed that corneal nerve contraction may persist even after completion of chemotherapy. In vivo, corneal confocal microscopy is useful for monitoring corneal health in chemotherapy patients [32].

Like other treatments, targeted therapy may have side effects, including those affecting the eye. However, it is generally considered more specific and less toxic than chemotherapy. The effects of targeted therapy on the eye depend on the specific drug and its mechanism of action. Targeted therapy is often associated with conjunctivitis and corneal lesions [33] and, in rare cases, can lead to eversion of the lower eyelid [34]. These side effects significantly limit patients' daily activities, causing difficulties with reading, driving, and recognizing faces, and sometimes from decreased vision [35] to vision loss [31] (Tables 1 and 3).

Table 3 – Main toxic effects of targeted therapy drugs on the visual organ

Preparations	Toxic effect on the organ of vision	Clinical manifestations	Notes
EGFR and FGFR inhibitors	Retinopathy, corneal ulceration	Damage to the corneal epithelium, deterioration of visual acuity	The process improved after treatment was stopped.
Vandetanib, Osimertinib, ABT-414, ASP-5878, FPA-144	Corneal epithelial lesion	Deterioration of visual acuity, changes in the corneal epithelium	Reversibility of changes after cessation of therapy
Belamaf	Microcystic epithelial changes of the cornea	Corneal changes with microcystic lesions both centrally and peripherally	Reversibility of changes after cessation of therapy

D. Barmas-Alamdari et al. described the case of a 59-year-old woman with metastatic breast cancer who developed crusting and a gritty sensation in both eyes. Ophthalmologic examination revealed multiple de-

fects, including corneal ulcers and ulcerations. The patient's eyes stabilized after discontinuing trastuzumab and treating the keratopathy [36].

Ophthalmological questionnaires.

In addition to ophthalmological complications, which can have a significant impact on the quality of life of patients receiving chemotherapy and targeted therapy, these treatments also have an impact on psychological health.

Patients often suffer from increased levels of depression, anxiety, and social isolation, which further impacts overall well-being and perceived quality of life [37, 38]. This is an important aspect to consider in a comprehensive assessment of the patient's condition during treatment.

Eye complications such as dry eyes, decreased vision, and other vision problems can increase anxiety and loneliness because they make it difficult to perform normal daily activities [37, 39–44].

In this context, introducing ophthalmological questionnaires and scales to assess the quality of life of patients undergoing chemotherapy is paramount.

These questionnaires allow an objective and quantitative assessment of treatment-related visual impairments and monitor the impact of visual impairments on patients' overall quality of life [45].

Questionnaires such as the National Eye Institute Visual Function Questionnaire (NEI VFQ-25)[46], Ocular Surface Disease Index (OSDI)[47], European Organization for Research and Treatment of Cancer Quality of Life questionnaires (EORTC-QLQ-C30 and EORTC-QLQ-MY20)[48] help to identify the most subtle changes in visual acuity and their changes.

Ophthalmological questionnaires such as OSDI and NEI-VFQ-25 can confirm the safety or risk of a drug for the eye by assessing eye symptoms and their impact on the patient's daily life [49]. They can detect changes in visual functions such as dryness, irritation, eye pain, and blurred vision. If the symptoms remain stable or improve during treatment, this may indicate the drug's safety. For example, in the study by R. Popat et al. within the DREAMM-2, questionnaires such as OSDI and NEI-VFQ-25 showed that visual impairment caused by benthamab was temporary. This confirms the drug's safety for the eye since most symptoms, such as temporary visual impairment, dryness, and eye pain, recovered within a few weeks without a long-term impact on the patients' quality of life [50].

VF-14 (Visual Function Index) questionnaire consists of 18 questions covering 14 types of daily visual activities. The results allow us to determine the patient's subjective assessment of visual functions.

The ADVS (Activities of Daily Vision Scale) includes 21 questions that assess aspects such as night and day vision, distance and near vision functions, and contrast perception. It was originally developed for cataract patients but can be adapted to assess other visual impairments.

An example of the application of these questionnaires is the study by J. Ma et al., who used two questionnaires to assess dry eye symptoms and adverse effects of cancer therapy in breast cancer patients: the OSDI and the National Comprehensive Cancer Network Breast Cancer Symptom Index-16 (NFBSI-16). The OSDI questionnaire was administered to all participants to assess the severity of dry eye, and the NFBSI-16 was administered specifically to those undergoing cancer treatment to assess therapy-related symptoms. The results showed that 59% of breast cancer patients undergoing chemotherapy or targeted therapy experienced symptomatic dry eye, which was significantly higher compared to 25.5% in the control group. The study highlights the importance of monitoring dry eye symptoms in patients receiving chemotherapy or targeted therapy and recommends early intervention to improve their quality of life during treatment. General questionnaires are also used to assess the quality of life of cancer patients: **FACT-G (Functional Assessment of Cancer Therapy – General),** designed for a general assessment of the quality of life of patients with cancer, covers physical, social, emotional and functional well-being; **EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire)** is a widely used tool for assessing the quality of life of cancer patients, including 30 questions covering various aspects of health and well-being. Regularly using these monitoring methods will allow for timely detection and correction of ophthalmological complications arising from chemotherapy, as well as ensuring optimal quality of life for patients.

Validation of dynamic assessment questionnaires designed specifically to assess vision-related quality of life in patients undergoing chemotherapy and targeted therapy will require additional research. Considering the complex interactions between variables affecting quality of life requires multidisciplinary strategies.

It is necessary to note the possible methods of correction of complications from the organ of vision during chemotherapy, which require a comprehensive approach to correction, including drug therapy, physiotherapeutic methods, and surgical interventions (Table 4).

General correction methods include dynamic monitoring (regular ophthalmologist examinations once every 3 months during chemotherapy), optical coherence tomography (OCT) is also performed to assess the retina and optic nerve condition, and fluorescent angiography to monitor vascular changes. It is necessary to correct chemotherapy doses in the treatment of the underlying disease in case of severe side effects and conduct maintenance therapy to reduce the toxic effects of drugs.

Table 4 – Methods of correction of complications from the organ of vision during chemotherapy

Correction form	Method
Correction of vascular disorders (angiospasm, retinopathy, retinal microangiopathy)	antioxidants and angioprotectors, drugs to improve vascular tone, corticosteroids (for severe retinal edema), physiotherapeutic methods (laser coagulation of the retina for diabetes-like changes, magnetic therapy to improve vascular tone)
Correction of neuropathies (retrobulbar neuritis, neuroretinitis)	neuroprotectors and B vitamins, glucocorticosteroids (for inflammatory changes), anticoagulants and antiplatelet agents, physiotherapeutic methods (electrical stimulation of the optic nerve, acupuncture to stimulate nerve activity)
Correction of dry eye and corneal lesions (keratopathy, epitheliopathy, dry eye syndrome)	artificial tears, anti-inflammatory agents, regenerating agents, antibacterial drops (if there is a risk of infection), physiotherapeutic methods (light therapy and laser stimulation of corneal regeneration)
Correction of central and peripheral visual impairments (central and paracentral scotoma, narrowing of visual fields)	retinal metabolism stimulants, drugs to improve hemodynamics, physiotherapeutic methods (laser exposure to the retina to stabilize the process, training using computer programs to restore visual fields)

Conclusion: Survival of patients with cancer has improved significantly due to the development of anti-cancer drugs, including systemic chemotherapeutic agents. However, long-term side effects, including visual impairment, can significantly affect the quality of life of these patients. The lack of specific recommendations for ocular monitoring during chemotherapy and targeted therapy exacerbates the problem, as such drugs can cause serious visual complications that remain underestimated.

Comprehensive correction of ophthalmological complications during chemotherapy should include drug therapy, physiotherapeutic methods, and regular vision monitoring. Early diagnosis and timely treatment help minimize the risks of persistent visual impairment and maintain patients' quality of life.

Dynamic quality of life assessment represents a promising approach to understanding and addressing visual impairment in patients receiving chemotherapy and targeted therapy. Given the temporal variations and contextual factors that influence quality of life, these methods open the door to personalized interventions that can improve treatment outcomes. As vision-specific quality-of-life assessment tools, Ophthalmology questionnaires have significant potential to improve care and well-being in this vulnerable patient population.

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АҢДАТПА

ХИМИОТЕРАПИЯ АЛҒАН НАУҚАСТАРДЫҢ КӨРУ ҚАБІЛЕТІНІҢ БҰЗЫЛУЫМЕН БАЙЛАНЫСТЫ ӨМІР САПАСЫН ДИНАМИКАЛЫҚ БАҒАЛАУ

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Өзектілігі: *Онкологиялық ауруларды емдеуде қолданылатын химиотерапия және мақсатты терапия жиі көру функциясына әсер ететін жанама әсерлерді тудырады. Мұндай асқынуларға құрғақ көз синдромы, катаракта, кератопатия, ретинопатия және басқалар жатады, бұл пациенттердің өмір сүру сапасын айтарлықтай нашарлатуы мүмкін. Бұл мақалада көру қабілетінің бұзылуы бар онкологиялық науқастардың өмір сапасын бағалауға және осы жанама әсерлерді бақылаудың маңыздылығына баса назар аударылады.*

Мақаланың мақсаты: *көру асқынуларының пайда болу уақытына, олардың ауырлығына және қайтымдылығына ерекше назар аудара отырып, химиялық және мақсатты терапияның әсерінен туындайтын көру қабілеті бұзылған онкологиялық науқастардың өмір сүру сапасын зерттеу.*

Әдістері: *Зерттеуге 2012-2024 жылдар аралығында PubMed, Embase, Cochrane Library, Scopus, Web of Science және Google Scholar дерекқорларында жарияланған орыс және ағылшын тілдеріндегі 65 ғылыми мақалаға талдау жасалды. Іздеу кезінде химиотерапия, көру уыттылығы және қатерлі ісікке қатысты негізгі сөздер қолданылды. Зерттеуге мета-талдаулар, жүйелі шолулар, бақыланатын клиникалық зерттеулер және жеке жағдай есептері кірді.*

Нәтижелері: *Цисплатин және паклитаксел сияқты химиотерапевтік препараттар құрғақ көз синдромы, қызыл көз, катаракта және ретинопатия сияқты көру бұзылыстарын тудырады. Бевацизумаб және эрлотиниб сияқты мақсатты препараттар қасаң қабықтың зақымдануын, конъюнктивит пен увеитті тудырады. Көру қабілетінің бұзылуы пациенттердің өмір сүру сапасын айтарлықтай нашарлатады, оқу, көлік жүргізу және бет-әлпетті тану сияқты күнделікті тапсырмаларды орындауда қиындықтар тудырады. Бұл бұзылулар сонымен қатар ыңғайсыздықты, құрғақ көзді, жасты тудырады және көру өткірлігінің төмендеуіне әкелуі мүмкін. Сирек жағдайларда мұндай бұзылулардың салдары көру қабілетінің ішінара немесе толық жоғалуына әкеледі, бұл пациенттің әлеуметтік жұмысына және эмоционалдық жағдайына елеулі әсер етеді. Арнайы офтальмологиялық сауалнаманы қолдану жанама әсерлерді ерте анықтауға мүмкіндік береді, бұл пациенттердің өмір сапасын жақсартуға көмектеседі.*

Қорытынды: *Өмір сүру сапасын динамикалық бағалау химиотерапия мен мақсатты терапияны алатын пациенттердегі көру қабілетінің бұзылуын түсінуге және шешуге перспективалы көзқарасты білдіреді. Өмір сапасына әсер ететін уақытша өзгерістер мен контекстік факторларды ескере отырып, бұл әдістер емдеу нәтижелерін жақсартатын жеке араласуға жол ашады.*

Түйінді сөздер: *химиотерапия, мақсатты терапия, көру қабілетінің бұзылуы, өмір сапасы.*

АННОТАЦИЯ

ДИНАМИЧЕСКАЯ ОЦЕНКА КАЧЕСТВА ЖИЗНИ, СВЯЗАННОГО С НАРУШЕНИЕМ ЗРЕНИЯ У БОЛЬНЫХ, ПОЛУЧАЮЩИХ ХИМИОТЕРАПИЮ

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Актуальность: *Химиотерапия и таргетная терапия, используемые при лечении рака, нередко сопровождаются побочными эффектами, которые затрагивают зрительную функцию. Среди таких осложнений – синдром сухого глаза, катаракта, кератопатия, ретинопатия и другие, которые могут значительно ухудшать качество жизни пациентов. В данной работе акцент сделан на оценке качества жизни онкологических больных, испытывающих зрительные нарушения, и важности мониторинга этих побочных эффектов.*

Цель исследования *– изучить качество жизни онкобольных с нарушениями зрения, возникающими в результате воздействия химио- и таргетной терапии, с особым акцентом на времени возникновения зрительных осложнений, их выраженности и обратимости.*

Методы: *В рамках исследования был проведен анализ 50 научных статей на русском и английском языках, опубликованных в базах данных PubMed, Embase, Cochrane Library, Scopus, Web of Science и Google Scholar с 2012 по 2024 годы. Для поиска использовались ключевые слова, связанные с химиотерапией, токсическими воздействиями на зрение и злокачественными новообразованиями. В исследование были включены метаанализы, систематические обзоры, контролируемые клинические испытания и индивидуальные клинические случаи.*

Результаты: *Химиотерапевтические препараты, такие как цисплатин и паклитаксел, вызывают зрительные нарушения, включая синдром сухого глаза, покраснение глаз, катаракту и ретинопатию. Таргетные препараты, такие как бевацизумаб и эрлотиниб, приводят к повреждениям роговицы, конъюнктивиту и увеиту. Зрительные нарушения значительно ухудшают качество жизни пациентов. Эти нарушения также вызывают дискомфорт, сухость в глазах, слезотечение и могут привести к снижению остроты зрения. В редких случаях последствия таких нарушений приводят к частичной или полной потере зрения, что серьезно сказывается на социальном функционировании и эмоциональном состоянии пациента. Использование специальных офтальмологических опросников позволяет на ранних стадиях выявить побочные эффекты, что способствует улучшению качества жизни пациентов.*

Заключение: *Динамическая оценка качества жизни представляет собой перспективный подход для понимания и решения проблемы зрительных нарушений у пациентов, получающих химиотерапию и таргетную терапию. Учитывая временные колебания и контекстуальные факторы, влияющие на качество жизни, эти методы открывают путь для персонализированных вмешательств, которые могут улучшить результаты лечения.*

Ключевые слова: *химиотерапия, таргетная терапия, нарушения зрения, качество жизни.*

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STUDY OF THE ONCOLOGICAL PROCESS INFLUENCE ON OVARIAN RESERVE

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ABSTRACT

Relevance: *The problem of reproductive health of women suffering from oncological diseases is becoming increasingly important in the context of modern healthcare. Breast cancer is increasingly diagnosed in young women of reproductive age, which creates a need to study the impact of these diseases on the ovarian reserve, which is critical for the ability to conceive.*

This study aims to *assess the impact of breast cancer on the ovarian reserve of women of reproductive age, as well as to develop strategies for preserving fertility.*

Methods: *The study involved 80 patients with oncological diseases and 61 conditionally healthy women in the Control Group. The ovarian reserve was assessed by ultrasound examination with antral follicle counting and hormonal status analysis (FSH, LH, AMH).*

Results: *The average number of antral follicles in the main group was lower (Me=6) compared to the Control Group (Me=9), which was statistically significant (p<0.001). FSH and AMH levels also showed sig-nificant differences between the groups, confirming the negative impact of cancer on the ovarian reserve. The LH level, however, remained stable in both groups (p=0.661).*

Conclusions: *The study showed that cancer significantly impacts the ovarian reserve, reducing women's reproductive capabilities. These data highlight the need to integrate fertility preservation strategies, including oocyte cryopreservation, into treatment programs. An interdisciplinary approach that combines the efforts of oncologists and reproductive specialists is important to achieve better clinical and personal outcomes for patients. Further research will help to deepen the understanding of the mechanisms affecting the ovarian re-serve in the context of cancer.*

Keywords: *breast cancer, ovarian reserve, hormonal status, fertility preservation, reproductive health.*

Introduction: The problem of reproductive health of women suffering from oncological diseases is becoming increasingly important in the context of modern healthcare [1]. Breast cancer is increasingly diagnosed in young women of reproductive age, which creates a need to study the impact of these diseases on the ovarian reserve, which is critical for the ability to conceive [2, 3]. Modern treatment methods such as chemotherapy and radiotherapy often cause a decrease in ovarian reserve, thereby jeopardizing the possibility of future pregnancy [4-8]. Studying the relationship between cancer and changes in ovarian reserve allows us to develop more accurate strategies for preserving fertility, which is important for improving patients' quality of life [9, 10].

This study aims to assess the impact of breast cancer on the ovarian reserve of women of reproductive age, as well as to develop strategies for preserving fertility.

Materials and Methods: The study involved 80 patients aged 18 to 45 with breast cancer who were diagnosed and treated at the Tashkent city branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (Tashkent, Uzbekistan). The Control Group included 61 conditionally healthy women of relevant ages. The ovarian reserve was assessed by ultrasound examination with antral follicle counting and hormonal status analysis (FSH, LH, AMH) before treatment. Laboratory studies were conducted in the private clinic "Mediopharm ECO" (Tashkent, Uzbekistan).

Table 1 provides descriptive statistics for categorical variables obtained in the study. Several key points regarding the distribution of participants across groups and tumor types will be emphasized.

The main study group consisted of 80 participants, which corresponds to 56.3% of the total number of those examined. The Control Group, which included 61 conditionally healthy patients, accounted for 43.7%. The study observations were characterized by an equal distribution between the group with breast cancer and the Control Group regarding representativeness.

This distribution suggests that the study is representative enough to allow comparison of data between patients with cancer and conditionally healthy participants. The categorical variables studied highlight the importance of understanding not only quantitative indicators but also qualitative characteristics of patients, which may have a significant impact on further analysis of ovarian reserve and hormonal status in the context of a particular disease.

Modern statistical methods were used to process and analyze the data. Descriptive statistics were presented as frequencies, percentages, and confidence intervals (95% CI). Groups were compared using the Mann-Whitney test for independent samples, where p-values less than 0.05 were considered statistically significant. All calculations were performed using statistical analysis software.

Table 1 – Descriptive statistics of the study's categorical variables

Indicators	Categories	Values		
		Abs.	%	95% CI
Research Group	Main Group	80	56.3	47.8-64.6
	Control Group	61	43.7	35.4-52.2
Tumor type	Breast Cancer	80	56.7	48.1-65.0
	Norm	61	43.3	35.0-51.9
Cancer Stage	I	22	15.6	10.0-22.7
	II	29	20.6	14.2-28.2
	III	20	14.2	8.9-21.1
	IV	9	6.4	3.0-11.8
	N	61	43.3	35.0-51.9

Results: According to Table 2, the mean age of the participants was 31 years, with a range of 18 to 45 years. The number of antral follicles ranged from 1 to 15; the median value was 6, and the interquartile range (IQR) was 4 to 9.

Table 2 – Analysis of the ovarian reserve indicator depending on the tumor type

Indicators	Categories	Tumor Type			p-value
		Me	Q_1-Q_3	n	
Antral follicle count	BC	6.00	3.00-8.00	80	<0.001*
	norm	9.00	5.00-11.00	61	
Follicule-Stimulating Hormone (mIU/ml)	BC	6.75	5.70-15.03	80	<0.001*
	norm	6.40	3.80-8.40	61	
Luteinizing Hormone (mIU/ml)	BC	5.35	4.20-12.00	80	0.543
	norm	5.40	4.60-6.30	61	
Anti-Mullerian Hormone (ng/ml)	BC	2.35	0.67-3.20	80	0.030*
	norm	2.70	1.30-3.90	61	

*Notes: BC – breast cancer; * – differences in indicators are statistically significant (p<0.05)*

The analysis showed that the number of antral follicles in patients with breast cancer was 6.00 (IQR = 3.00-8.00) among 80 participants. In the Control Group, including women with normal ovarian reserve, a median of 9.00 (5.00-11.00) with 61 participants. Statistical analysis revealed significant differences between the groups ($p < 0.001$), indicating a weakening of the ovarian reserve in patients with breast cancer.

The FSH level in women with breast cancer was 6.75 mIU/ml (5.70-15.03), while in the Control Group, it was 6.40 mIU/ml (3.80-8.40). Statistically significant differences were also found (p<0.001), indicating that the presence of cancer can negatively affect the hormonal background and change the functioning of the ovaries.

For the LH indicator, the results were 5.35 mIU/ml (4.20-12.00) for the BC group and 5.40 mIU/ml (4.60-6.30) for the norm. Here, statistically significant differences were not found (p=0.543), which may indicate a stable LH level despite a malignant process.

As for AMH, the median for patients with breast cancer was 2.35 ng/ml (0.67-3.20), while for the Control Group, it was 2.70 ng/ml (1.30-3.90). In this case, statistically significant differences were also found (p=0.030), confirming the decrease in AMH levels in cancer patients and indicating possible depletion of the ovarian reserve.

We analyzed the ovarian reserve indicator depending on the cancer stage.

Significant results were obtained as part of the analysis of ovarian reserve indicators depending on the breast cancer stage, presented in Table 3. Thus, the study showed that the disease stage significantly affects various ovarian reserve parameters.

According to the number of antral follicles, it was found that in Stage I, the median was 6.00 (IQR=5.00-8.00) in 22 patients. In Stage II, this indicator was higher, at 7.00 (5.00-9.00), in 29 participants. However, in Stages III and IV the number of antral follicles decreased to 4.00 (2.00-7.00) and 4.00 (1.00-6.00) in 20 and 9 patients, respectively. These results indicate statistically significant differences between the stages (p<0.001), which indicates increasing depletion of the ovarian reserve with disease progression.

FSH showed a similar trend: at Stage I, the level was 6.60 mIU/ml (5.62-13.92), and at Stage II – 6.10 mIU/ml (5.50-10.10). However, the FSH levels at Stages III and IV increased significantly – to 13.35 mIU/ml (6.30-15.93) and 13.50 mIU/ml (6.40-18.00), respectively. These results also demonstrated statistically significant differences (p = 0.001), indicating that FSH level increases with cancer progression, which may indicate ovarian dysfunction.

According to the LH level at Stage I, the median was 5.10 mIU/ml (4.17-7.83) and Stage II – 4.80 mIU/ml (4.10-5.80). At Stages III and IV, the LH level increased to

11.00 mIU/ml (5.30-13.70) and 9.00 mIU/ml (5.10-12.50), respectively, which also confirmed the statistical significance of the differences (p=0.015). An increase in LH levels with disease progression may reflect the body's adaptation mechanisms to changes in ovarian function.

Table 3 – Analysis of the ovarian reserve indicator depending on the cancer stage

Indicators	Cancer stage	stage			p
		Me	Q_1-Q_3	N	
Antral follicle count	I	6.00	5.00-8.00	22	<0.001* pN-I=0.020pN-III<0.001pN-IV=0.004
	II	7.00	5.00-9.00	29	
	III	4.00	2.00-7.00	20	
	IV	4.00	1.00-6.00	9	
	N	9.00	5.00-11.00	61	
Follicule-Stimulating Hormone (mIU/ml)	I	6.60	5.62-13.92	22	0.001* pN-III=0.005pN-IV=0.041
	II	6.10	5.50-10.10	29	
	III	13.35	6.30-15.93	20	
	IV	13.50	6.40-18.00	9	
	N	6.40	3.80-8.40	61	
Luteinizing Hormone (mIU/ml)	I	5.10	4.17-7.83	22	0.015* pIII-II=0.021
	II	4.80	4.10-5.80	29	
	III	11.00	5.30-13.70	20	
	IV	9.00	5.10-12.50	9	
	N	5.40	4.60-6.30	61	
Anti-Mullerian Hormone (ng/ml)	I	2.40	0.93-3.35	22	0.024*
	II	3.00	1.80-3.30	29	
	III	0.90	0.50-2.82	20	
	IV	0.90	0.40-2.60	9	
	N	2.70	1.30-3.90	61	

*Notes: * – differences in indicators are statistically significant (p<0.05)*

As for AMH, its levels were 2.40 ng/ml (0.93-3.35) at Stage I and 3.00 ng/ml (1.80-3.30) at Stage II and decreased to 0.90 ng/ml (0.50-2.82) and 0.90 ng/ml (0.40-2.60) at Stage III and IV, respectively. These results also showed statistically significant differences (p=0.024), confirming that AMH levels significantly decrease at late stages of the disease, indicating depletion of ovarian reserve.

Thus, the data show that breast cancer progression negatively affects all the studied parameters of ovarian reserve. A decrease in the number of antral follicles and AMH levels, as well as an increase in FSH and LH levels at later stages of the disease, emphasize the need for special attention to the state of reproductive function in women with cancer. These results may be useful for clinical monitoring and treatment planning, as well as for discussing fertility issues with patients.

Discussion: The study results revealed a negative impact of oncological diseases on the ovarian reserve. A significant decrease in the number of antral follicles in the participants of the main group, compared with the Control Group, indicates possible damage to the ovarian tissue due to either the disease itself or aggressive treatment. This was reflected most of all in the indicators of the number of antral follicles and the levels of FSH and AMH hormones. The FSH level was significantly higher in patients with oncological diseases, which may indicate insufficient ovarian function and compensatory mechanisms of the body to stimulate follicular growth.

The observed differences in AMH levels also confirm the deterioration of the ovarian reserve since this Hormone correlates with the number of antral follicles and is considered an important biomarker of reproductive health. Interestingly, the LH level remained stable, which may indicate a selective lesion of the follicle-stimulating system in the ovaries without affecting the hypothalamic-pituitary mechanisms regulating LH production.

Conclusion: The impact of cancer on ovarian reserve significantly limits women's future reproductive options. These findings are important for the development of fertility programs that may include oocyte cryopreservation prior to aggressive treatment or the use of ovarian protection methods during therapy. The study highlights the need for a multidisciplinary approach in treatment planning, with oncologists, reproductive specialists, and psychologists working together to ensure patients' best clinical and personal outcomes.

Thus, the analysis shows that oncological diseases significantly affect ovarian reserve indicators such as the number of antral follicles, FSH, and AMH levels. It is important to take these differences into account when planning treatment and maintaining reproductive func-

tion in women who have breast cancer. It is also necessary to continue research to understand the mechanisms affecting ovarian reserve and hormonal status in women with oncological diseases.

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АҢДАТПА

ОНКОЛОГИЯЛЫҚ ПРОЦЕСТІҢ АНАЛЫҚ СҮТ БЕЗ ҚОРЫНА ӘСЕРІН ЗЕРТТЕУ

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Өзектілігі: *Онкологиялық аурулардан зардап шегетін әйелдердің репродуктивті денсаулығы мәселесі заманауи денсаулық сақтау тұрғысынан айтарлықтай өсуде. Сүт безі қатерлі ісігі репродуктивті жастағы жас әйелдерде жиі диагноз қойылады, бұл онкологиялық аурулардың жүктілік қабілеті үшін маңызды аналық бездердің резервіне әсерін зерттеу қажеттілігін тудырады. Сүт безі қатерлі ісігі репродуктивті жастағы жас әйелдерде диагноз қойылады, бұл қатерлі ісік ауруының аналық сүт без қорына әсерін зерттеу қажеттілігін тудырады, бұл жүктілік қабілетіне өте маңызды.*

Зерттеудің мақсаты *– репродуктивті жастағы әйелдердің аналық без қорына сүт безі қатерлі ісігінің әсерін бағалау, сондай-ақ құнарлылықты сақтау стратегияларын әзірлеу.*

Әдістері: *Зерттеуде 80 онкологиялық аурулардан зардап шегетін науқастар және бақылау тобында 61 шартты сау науқастар қатысты. Аналық сүт без қорын бағалау үшін антральды фолликулалар санын есептеу және гормоналды (ФЫГ, ЛГ, АМГ) мәртебені талдау үшін УДЗ қолданылған.*

Нәтижелері: *Негізгі топтағы антральды фолликулалардың орташа саны (ME=6) бақылау тобымен салыстырғанда (ME=9) төмен болды, бұл статистикалық маңызды болды (p<0,001). ФЫГ және АМГ деңгейлері сонымен қатар онкологиялық аурулардың аналық без қорына теріс әсерін растайтын топтар арасында айтарлықтай айырмашылықтарын көрсетті. Алайда ЛГ деңгейі екі топта да тұрақты болып қалды (p=0.661).*

Қорытынды: *Зерттеу онкологиялық аурулардың аналық без қорына айтарлықтай әсер ететінін, әйелдердің репродуктивті мүмкіндіктерін төмендететінін көрсетті. Бұл мәліметтер құнарлылықты, оның ішінде ооцит криоконсервингті және емдеу бағдарламаларын қолдау үшін стратегияларды біріктіру қажеттілігін көрсетеді. Онкологтар мен репродуктологтардың күш-жігерін біріктіретін пәнаралық тәсіл науқастар үшін ең жақсы клиникалық және жеке нәтижелерге қол жеткізу үшін маңызды. Әрі қарай зерттеулер онкологиялық аурулар аясында аналық сүт без қорына әсер ететін механизмдерді түсінуді тереңдетуге көмектеседі.*

Түйінді сөздер: *сүт безі қатерлі ісігі, аналық сүт без қоры, гормоналды жағдай, құнарлылықты сақтау, репродуктивті денсаулық.*

АННОТАЦИЯ

ИЗУЧЕНИЕ ВЛИЯНИЯ ОНКОЛОГИЧЕСКОГО ПРОЦЕССА НА ОВАРИАЛЬНЫЙ РЕЗЕРВ

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Актуальность: *Проблема репродуктивного здоровья женщин, страдающих онкологическими заболеваниями, приобретает всё большую значимость в контексте современного здравоохранения. Рак молочной железы всё чаще диагностируют у молодых женщин репродуктивного возраста, что вызывает потребность в изучении влияния онкологических заболеваний на овариальный резерв, критически важный для способности к зачатию.*

Цель исследования *– оценить влияние рака молочной железы на овариальный резерв женщин репродуктивного возраста, а также разработать стратегии по сохранению фертильности.*

Методы: *В исследовании участвовали 80 пациенток с онкологическим заболеванием и 61 условно здоровая женщина в контрольной группе. Для оценки овариального резерва применялись УЗИ для подсчета количества антральных фолликулов и анализ гормонального статуса (ФСГ, ЛГ, АМГ).*

Результаты: *Среднее количество антральных фолликулов в основной группе оказалось ниже (Me=6) по сравнению с контрольной (Me=9), что было статистически значимо (p<0,001). Уровни ФСГ и АМГ также продемонстрировали значительные различия между группами, подтверждая негативное влияние онкологических заболеваний на овариальный резерв. Уровень ЛГ, однако, оставался стабильным в обеих группах (p=0,661).*

Заключение: *Исследование показало, что онкологические заболевания оказывают значительное влияние на овариальный резерв, снижая репродуктивные возможности женщин. Эти данные подчеркивают необходимость интеграции стратегий сохранения фертильности, включая криоконсервацию ооцитов, в программы лечения. Междисциплинарный подход, объединяющий усилия онкологов и репродуктологов, важен для достижения лучших клинических и личностных результатов для пациенток. Дальнейшие исследования помогут углубить понимание механизмов, влияющих на овариальный резерв на фоне онкологических заболеваний.*

Ключевые слова: *рак молочной железы, овариальный резерв, гормональный статус, сохранение фертильности, репродуктивное здоровье.*

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THE RELATIONSHIP OF HUMAN EPIDERMAL GROWTH FACTOR-2 RECEPTOR EXPRESSION IN GASTRIC CANCER WITH AGE, GENDER, STAGE AND DEGREE OF TUMOR DIFFERENTIATION

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АННОТАЦИЯ

Relevance: *Gastric cancer is a heterogeneous malignant disease. In carcinomas, HER2 functions as an oncogene, primarily due to high gene amplification, which leads to protein overexpression in the cell membrane, enhancing malignant cell properties. Identifying new and effective biomarkers is essential for improving gastric cancer diagnosis, refining prognostic accuracy, predicting disease progression, and developing more effective patient treatment strategies.*

The study aimed to *assess the correlation between HER2 expression in gastric cancer and key clinical factors, including age, gender, disease stage, and tumor differentiation degree.*

Methods: *This comparative descriptive study analyzed surgical specimens from 109 patients with gastric cancer (stages 0- IIIC) collected from the pathology department of Marat Ospanov West Kazakhstan Medical University (WKMU) Medical Center following gastric cancer surgeries performed between 2021 and 2022. Histological and immunohistochemical studies were conducted in the morphological laboratory of the WKMU Department of Histology. The collected data underwent statistical processing.*

Results: *In the present study, the rates of positive Her2/neu expression in GC statistically significantly differed depending on the age (p=0.026) and gender (p=0.023) of the patient but did not statistically significantly differ depending on the localization, histopathological differentiation of the tumor, and the stage of the disease.*

Conclusions: *Considering the tendency towards the significance of positive expression of Her2/neu in low-differentiated gastric cancer (50%) and stages II-III of the disease, the Her2/neu marker can be considered as a potential therapeutic target that requires preliminary testing when prescribing targeted therapy.*

Keywords: *gastric cancer, morphology, histology, immunohistochemistry, Her2/neu.*

Introduction: Gastric cancer (GC) is a heterogeneous malignant disease. In various forms of GC, such as carcinoma, several HER2 biomarkers act as an oncogenic factor based on high gene amplification with transition to a malignant cell. In 2022, Zh.E. Komekbay et al. noted that "overexpression of the protein occurs on the cell membrane surface when using the Her2/neu marker. Previously, we reviewed the literature on using and identifying new and effective biomarkers to improve the diagnosis of gastric cancer, more accurately determine the prognosis, predict pathogenesis, and establish a new and effective treatment option for patients with GC" [1].

Researcher N.D. Bakirov [2] noted that solving the problem "will improve the results of complex treatment of gastric cancer in both early and widespread, disseminated forms." Earlier in their work in 2015, L.A. Naumova and O.N. Osipova explained: "Understanding the biology of cancer is being formed today by integrating gene expression data with the network of molecular interactions" [3].

According to N.D. Bakirov, GC includes a complex of genetic disorders that determine the property of uncontrolled growth and the ability to metastasize [2], while L.A. Naumova and O.N. Osipova point to a heterogeneous disease with various molecular and histological subtypes [3]. Biomarker tests are also reliable methods for detecting precancerous lesions of the stomach. Endoscopic screening is still the gold standard for diagnosing GC [4]. The role of HER2 in developing many types of cancer in humans was noted by K. Mandleywala et al.: "Antibody-based imaging strategies specific for certain GCs overexpressing the antigen allow visualization of primary tumors and metastases with high contrast. In this context, PET antibodies and SPECT antibodies have the potential advantage of noninvasively detecting changes in antigen expression (e.g., HER2) and target interactions in both the primary tumor and metastases. The novel integration of fluorescence-labeled antibodies and confocal laser endoscopy for rapid visualization of dynamic molecular signatures also represents a promising avenue toward personalized therapy" [5].

An analysis of the available literature showed that overexpression of Her2/neu is associated with a poor prognosis in male patients with proximal GC localiza-

tion, intestinal type of tumor in the late stages of the disease, with metastasis to the lymph nodes, as well as with well-differentiated GC with distant metastases [2, 6].

Furthermore, Her2/neu expression results were quantitatively higher in Asian studies compared to European ones. Y. Y. Lei et al. (2017) showed that the level of HER2 expression in Asians may be higher than in Europeans and proposed a convenient way to select patients for appropriate HER2 detection and subsequent treatment [6].

Later, in 2019, M Smolińska et al. found that HER2 and SATB1 are overexpressed in gastric cancer tumor tissues compared to normal gastric mucosa. The expression of the former protein was observed to differ depending on some clinicopathological features but without statistical significance, while the expression of the latter protein was not significantly associated with any of them [7].

As noted by several researchers, the overall reliability of immunohistochemical (IHC) assessment of HER2 may be affected by various preanalytical, analytical, and postanalytical variations, as discussed earlier. Thus, GC requires a standardized, unified system for assessing the IHC expression of HER2 and an expert interpretation of these data [8].

Other authors note that "the compatibility rate of IHC and fluorescence in situ hybridization (FISH) results was more than 90%. However, according to the literature, the false-negative rate in mucosal biopsy was low. IHC should be applied to the entire tumor area to exclude false-negative results due to tumor heterogeneity. HER-2/neu gene amplification correlated with the histological type of the tumor. Six of 21 cases in which FISH analysis was performed were of the diffuse type, and all of them were FISH-negative. Nine (60%) of 15 cases with the intestinal type were FISH+ (p=0.019)" [9].

HB Wang et al. showed that according to the ToGA study, HER2 positivity was either IHC3 (+) or IHC2 (+) with DISH (+). There was no relationship between HER2 positivity and the depth of tumor invasion and venous and lymphatic invasion (p>0.05). However, in men with intestinal-type cancer and moderately/well-differentiated GC, the frequency of HER2-positivity was higher than in women with diffuse/mixed type and poorly differentiated cancer [10].

The DI Park et al. study showed that the frequency of HER-2/neu amplification in intestinal-type cancer was higher than in diffuse-type cancer (P < 0.05). Tumors with HER-2/neu amplification were associated with low median survival (922 versus 3243 days) and 5-year survival (21.4% versus 63.0%; P < 0.05). According to the authors, using multivariate analysis, it was found that age, TNM stage, and HER-2/neu amplification were independently associated with survival. HER-2/neu amplification may be an independent prognostic factor in patients with GC, and patients with HER-2/neu amplification may be potential candidates for new adjuvant therapy, including humanized monoclonal antibodies [11].

Y. Li et al. proposed a prognostic model for HER2 status in resectable GC using contrast-enhanced multiphase CT images and serum tumor markers. "We found that arterial phase enhancement ratio, intratumoral necrosis, tumor margin, and CA125 level were independent risk factors for positive HER2 expression in GC" [12].

As early as 2022, D Bao et al. stated that "the prediction model built based on preoperative tumor invasion and serum markers CA125 and CA72-4 demonstrates high specificity and accuracy concerning the incidence of peritoneal dissemination. We expect that the results of our study can provide clinical value for preoperative assessment of patients with GC and selection of individual treatment for patients" [13].

Iranian scientists A. Feizy et al. noted a significant relationship in positive HER2/neu gene expression between men and women (46.2% in men versus none in women) (p<0.05) [14]. This study showed no statistical differences between the two groups of patients with and without HER2 overexpression in variables such as survival, histopathological type of cancer (according to Lauren classification), and primary anatomical site of the tumor. It was also noted that the results revealed a very close (p=0.051) association between HER2 expression and tumor grade. This association may be statistically insignificant but appears to be clinically important. Moreover, the results of the current study differed from those of other studies, especially in non-Iranian patients. The authors strongly recommend that future studies focus on the race of patients with a more accurate assessment of HER2 expression status and its polymorphisms. The authors argue that due to the genetic diversity of patients, it is better to conduct a meta-analysis within the same race or at least with geographic restrictions [14].

Earlier, in our work (Zh.E. Komekbay, G.A. Temirova), GC revealed a close relationship between the expression of Ki-67 and the degree of histopathological differentiation of the tumor (P=0.039). However, it was not possible to establish a statistically significant difference with age (p=0.664), patient gender (P=0.928), tumor localization (p=0.860), and disease stage (p=0.894). Thus, the appropriateness of targeted therapy in GC is based on the results of histological and IHC studies of the contents of the tumor material [15].

Tumor marker levels vary with different diseases; the result may be false negative or false positive.

The study aimed to assess the correlation between HER2 expression in gastric cancer and key clinical factors, including age, gender, disease stage, and tumor differentiation degree.

Materials and methods: The study was conducted on a cohort of patients with gastric cancer previously selected to analyze the expression of the Ki-67 marker [15].

Study design: This comparative descriptive study was conducted following the biostatistics and clinical epidemiology sector protocol of West Kazakhstan Marat Ospanov Medical University (WKMU). The WKMU Local Bioethics Commission has approved the choice of material and research methods (Protocol No. 8, dated October 15, 2021).

General population: Continuous sample. Surgical material was collected from 109 patients with various forms of stage 0-IIIC gastric cancer after surgeries for this disease from the WKMU Pathology Department in 2021-2022. *Inclusion criteria:* Patients of all ages operated on for stage 0-IIIC gastric cancer. *Exclusion criteria:* stage IV gastric cancer, as well as the presence of any other malignant neoplasms [15].

Research methods: Histological and IHC studies were performed in the morphological laboratory of the WKMU Department of Histology. The study followed the SOP "I ZKMU 65-03" of 01/10/2020. When determining the area of the anatomical location of the tumor (cardiac section, body, fundus, antral or pyloric section), we were guided by the WHO recommendations and the clinical protocol for RZh No. 174 dated 11/21/2022 of the Joint Commission on the Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan [15].

The work presents a comparative analysis of gastric cancer cases according to the histopathological classification of gastric tumors: G1 (highly differentiated), G2 (moderately differentiated), G3 (poorly differentiated), and G4 (undifferentiated) [15].

The surgical material was fixed in 10% buffered formalin. A sled microtome was used to prepare histological sections. After the paraffinization stage, histological sections of the stomach with a thickness of 4-5 μm were prepared from paraffin blocks [16]. The micro preparations were stained with hematoxylin and eosin to confirm that the cuttings were gastric tissue. The material was evaluated using an AxioLab A1 laboratory medical video microscope (Carl Zeiss Microscopy GmbH, Germany) at different magnifications (×50, ×100, ×400, ×1000) [15].

To study the proliferative activity, monoclonal rabbit antibodies RMab (clone: RBT-Her2) to Her2 and the Mouse/ Rabbit PolyDetector Plus DAB HRP Brown Detection System (Immuno DNA Washer 20x, Tinto Deparaffinator EDTA 20x (Bio SB, Santa Barbara, CA, USA) were used. All reagents were stored at 4°C before use. IHC analysis was performed using the detection system according to the manual IHC staining protocol. Stained sections were assessed at a high magnification of 400x, and 100 cells were counted in each field. In this case, 5 fields for each section were randomly selected and examined, and the number and intensity of positively stained cells were recorded and averaged [15].

The level of Her2neu expression positivity was defined according to the National Comprehensive Cancer Network (NCCN) guidelines [17]. HER2 expression was graded as 3+ with intense continuous membranous staining in more than 10% of tumor cells, 2+ corresponded to moderate continuous membranous staining in more than 10% of cells or intense continuous membranous staining in less than 10% of cells [15]. Grade 1+ was assigned to weak discontinuous membranous staining in more than 10% of cells. Grade 0 corresponded to observations where weak membranous staining was less than 10% of cells or absent. Grades 2+ and 3+ were classified as HER2 overexpression. Microscopic slides with a known, verified result of HER2 overexpression served as external controls [18, 19].

Statistical processing of the obtained results was performed using the Statistica 10 computer software system (StatSoft Inc., USA) and SPSS 25 with a 95% confidence interval (CI). The studied nonparametric groups were analyzed using the Mann-Whitney, Student's t-test, and Pearson's chi-square tests. StatTech v.3.0.9 (StatTech LLC, Russia) was used for statistical analysis. Quantitative indicators with normal distribution are described using arithmetic means (M) and standard deviations (SD), 95% CI. Quantitative data were calculated without normal distribution using the median (Me), lower, and upper quartiles (Q1-Q3). A comparison of percentages in the analysis of multifield contingency tables was performed using the Pearson chi-square test [15].

Results: A total of 109 cases of GC were included in the study, including 77 men (70.6%) and 32 women (29.4%). The age of patients at diagnosis ranged from 27 to 81 years (median: 63 years) (Table 1).

Table 1 – Age of patients (descriptive statistics of quantitative variables)

Indicator	Median, Me	Quartile, Q_1-Q_3	Sample size, n	Minimum range, min	Maximum range, max
Age	63	59-70	109	27	81

Tumors were predominantly found in the body of the stomach (47.7%) and less often in the cardiac (38.5%) and antral (13.8%) sections. According to the histopathological classification of gastric cancer, the following types of tumors were identified: highly differentiated – 4 (3.7%), moderately differentiated – 27 (24.8%), poorly differentiated – 46 (42.2%), and undifferentiated – 32 (29.4%).

In this study, cases of gastric cancer were distributed according to the TNM classification as follows: stage I – 6 (5.5%), stage II – 45 (41.3%), and stage III – 58 (53.2%) [15].

The level of Her2/neu expression showed "no membrane reactivity" in 57 (52.3%) cases, "+" weak or barely noticeable membrane reactivity – in 19 (17.4%), "++" "moderate or lateral membrane" reaction – in 21 (19.3%) and "+++," which means "complete basolateral" expression – only in 12 (11.0%) cases (Table 2).

As shown in Table 3 and Figure 1, statistically significant differences in Her2 expression levels were found depending on age (p=0.026) (method used: Mann-Whitney U test) [15].

Table 2 – Clinicopathological data and HER2 marker expression (descriptive statistics of categorical variables)

Indicator	Category	Abs.	Percent (%)	Confidence interval (95% CI)
Gender (F, M)	wives	32	29.4	21.0-38.8
	husband	77	70.6	61.2-79.0
Tumor localization	cardiac section	42	38.5	29.4-48.3
	body of the stomach	52	47.7	38.1-57.5
	antral and pyloric sections	15	13.8	7.9-21.7
Histopathological differentiation (high G1, medium G2, low G3, non-differentiable G4)	G1	4	3.7	1.0-9.1
	G2	27	24.8	17.0-34.0
	G3	46	42.2	32.8-52.0
	G4	32	29.4	21.0-38.8
pTNM stage (I, II, III)	I	6	5.5	2.0-11.6
	II	45	41.3	31.9-51.1
	III	58	53.2	43.4-62.8
Her2 expression	negative (-; +)	76	69.7	59.2-77.3
	positive (++; +++)	33	30.3	22.7-40.8

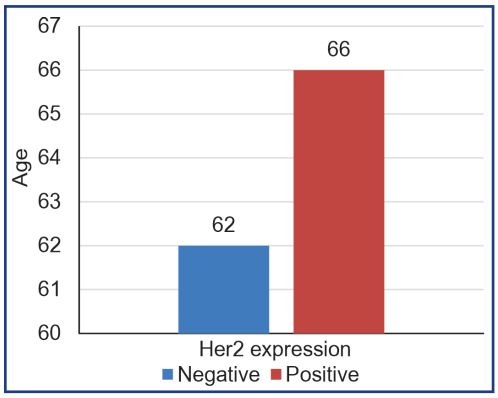

Figure 1 – The ratio of the parameters "Age" and "Her2 expression (negative, positive)" in gastric cancer

Table 3 – Her2 expression (negative, positive) depending on the patient's age

Indicator	Categories	Age			Significance level, p
		Median, Me	Quartile, Q_1-Q_3	Sample size, n	
Her2 expression	negative	62	54-69	75	0.026*
	positive	66	62-72	34	

*Note: * – differences in indicators are statistically significant (p<0.05)*

As shown in Table 4 and Figure 2, statistically significant differences in Her2 expression levels were found depending on gender (p=0.023) (method used: Pearson Chi-square) [15].

Comparison of tumor localization and Her2 expression levels (negative, positive) using the Pearson Chi-square method did not show statistically significant differences (p=0.148) (Table 5, Figure 3) [15].

Comparison of histopathological differentiation indices and Her2 expression (negative, positive) using the Pearson Chi-square method did not show statistically significant differences (p=0.441) (Table 6, Figure 4).

Comparison of tumor staging and Her2 expression (negative, positive) did not show significant differences (p=0.683) (Table 7, Figure 5).

Table 4 – Her2 expression level (negative, positive) in gastric cancer depending on the patient's gender

Indicator	Categories	Her2 expression		Significance level, p
		negative	positive	
Floor (F, M)	wives	17 (22.7)	15 (44.1)	0.023*
	husband	58 (77.3)	19 (55.9)	

*Note: * – differences in indicators are statistically significant (p<0.05)*

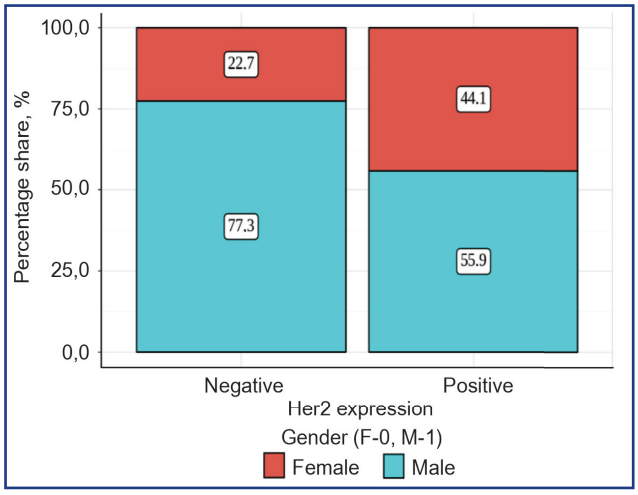

Figure 2 – Ratio of Her2 expression rates (negative, positive) depending on the patient's gender in gastric cancer

Table 5 – Her2 expression level (negative, positive) in gastric cancer depending on tumor location

Indicator	Categories	Her2 expression		Significance level, p
		negative	positive	
Tumor localization	cardiac section	33 (44.0)	9 (26.5)	0.148
	body of the stomach	34 (45.3)	18 (52.9)	
	pyloric and antral sections	8 (10.7)	7 (20.6)	

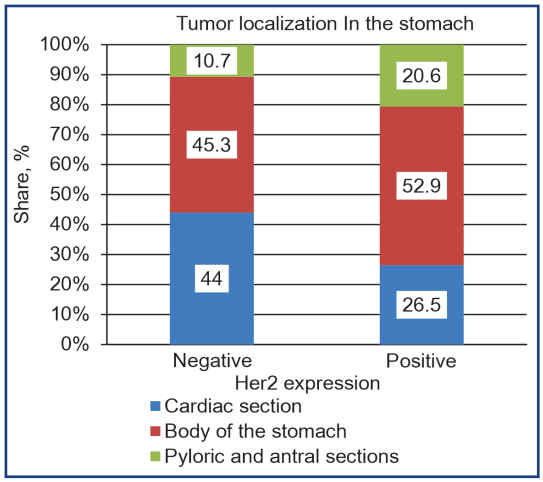

Figure 3 – The ratio of the indicators "Tumor localization" and "Her2 expression (negative, positive)" in gastric cancer

Table 6 – Her2 expression level (negative, positive) in gastric cancer depending on the histopathological differentiation of the tumor

Indicator	Categories	Her2 expression		Significance level, p
		negative	positive	
Histopathological differentiation of the tumor (high – G1, medium – G2, low – G3, undifferentiated – G4)	G1	2 (2.7)	2 (5.9)	0.441
	G2	19 (25.3)	8 (23.5)	
	G3	29 (38.7)	17 (50.0)	
	G4	25 (33.3)	7 (20.6)	

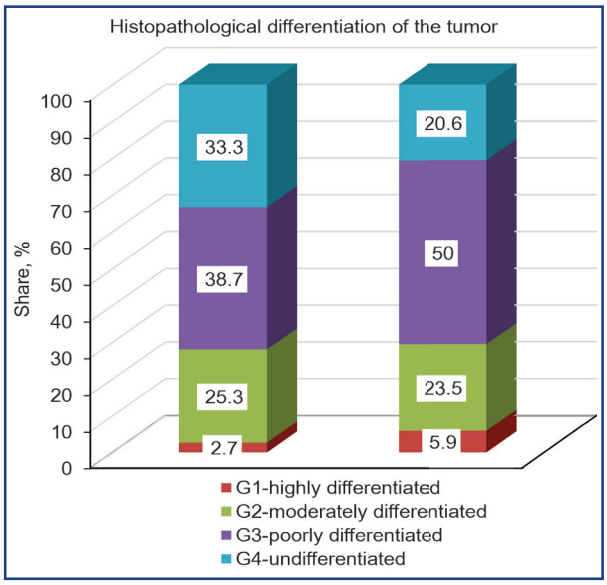

Figure 4 – Histopathological differentiation of gastric cancer depending on the indicator "Her2 expression (negative, positive)"

Table 7 – Expression level of the Her2 marker in gastric cancer

Indicator	Categories	Her2 expression		Significance level, p
		negative	positive	
pTNM stages	I	4 (5.3)	2 (5.9)	0.683
	II	29 (38.7)	16 (47.1)	
	III	42 (56.0)	16 (47.1)	

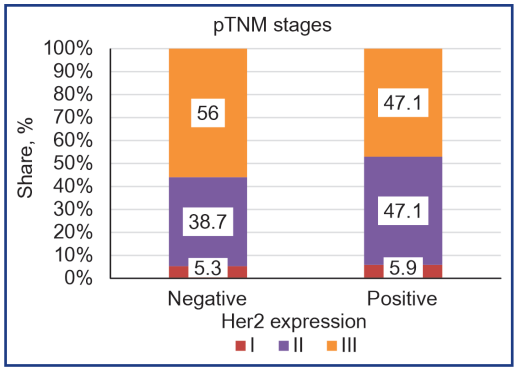

Figure 5 – The proportion of cases of gastric cancer by stage of the disease depending on the indicator "Her2 expression (negative, positive)"

Discussion: Z. Wei et al. noted that "in non-metastatic gastric adenocarcinoma, Her2 expression and the combined expression of Her2 and Ki-67 were associated with several clinicopathological factors including tumor differentiation and stage, and only +++ Her2 expression was associated with worse prognosis in multivariate analysis with marginal significance in their study, whereas Ki-67 alone had limited clinicopathological and prognostic value" [20]. HER2 overexpression results in the receptors transmitting excessive signals for cell proliferation to the nucleus. It has been suggested that HER2-positive cells directly contribute to tumors' pathogenesis and clinical aggressiveness. In 2020, researchers from the University of South China (Ye D.M., Xu G., Ma W., Li Y., Luo W., Xiao Y., Liu Y., and Zhang Z.) noted that "identification of new and effective biomarkers is necessary to improve the diagnosis of gastric cancer in order to increase the accuracy of gastric cancer diagnosis, determine prognosis and predict pathogenesis…" [21].

HER2 overexpression in gastric cancer is associated with poor prognosis. Thus, according to M. Razmi et al., the detection of tumor cell markers is mainly associated with worse treatment outcomes in patients with gastric cancer, both overall and individually. Detection of a combined marker panel may be useful as a prognostic marker for determining tumor aggressiveness and poor prognosis in patients with gastric cancer, which will likely identify new potential targets for therapeutic approaches [22].

HER2 expression in gastric cancer has been known for many years. In addition to its involvement in cancer pathogenesis, HER2 has also been evaluated in targeted therapy. HER-2 is currently considered a potential therapeutic target requiring preliminary testing for HER2 status. In 2018, Malaysian researchers P. Rajadurai et al. indicated that HER2 overexpression was significantly more common (p<0.001) in diffuse-type tumors (39.8%) than in intestinal-type tumors (14.9%) [23]. Egyptian researchers R.A. Abdel-Salam et al. noted a high frequency of HER2/neu-positivity in resectable gastric carcinomas (about 54%). The only statistically significant association was found between positive Her2/neu expression and the intestinal Lauren type [24]. In our study, the overall HER2 positivity rate was 30.3%. At the same time, in the work of A. Shabbir et al . HER2 was significantly expressed in poorly differentiated GC, mainly observed in women aged >60 years and stage IIIC tumors [25], whereas according to Y. Lei et al. HER2 overexpression correlated with various clinicopathological parameters in patients with GC: male gender, proximally located tumor, and poorly differentiated tumor [6]. In our study, there was a statistically significant association between HER2 positive expression and the age of patients, who were predominantly observed at the age <66 (p=0.026), and statistically significant differences (p=0.023) were also established when assessing the "sex of patients" parameter. However, we did not find any significant correlation between HER2 overexpression and tumor localization, histopathological differentiation of the tumor, and the stage of the disease according to TNM. There is a tendency towards the significance of HER2, positive expression in poorly differentiated GC (50%) and stage II-III of the disease. Many authors did not report any significant association between tumor localization and HER2 positivity, and conflicting results were reported regarding tumor localization and HER2 expression. In our study, tumors located in the body of the stomach account for 52.9% of cases, which may be the reason for a higher rate of HER2 positivity (p=0.148), although this indicator is statistically insignificant.

Conclusion: In this study, the dependence of HER2 marker expression on age, gender, disease stage, and differentiation degree was determined in 109 patients operated on for stage 0-IIIC gastric cancer. Thus, positive HER2/neu expression in gastric cancer depends on the age (p=0.026) and gender (p=0.023) of the patient but does not depend on the localization and histopathological differentiation of the tumor and the stage of the disease. Considering the positive expression of HER2/neu in poorly differentiated gastric cancer (50%) and stages II-III of the disease, this marker can be considered as a potential therapeutic target that requires preliminary testing when prescribing targeted therapy.

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АҢДАТПА

АСҚАЗАННЫҢ ҚАТЕРЛІ ІСІГІНДЕ АДАМНЫҢ ЭПИДЕРМАЛЫҚ ӨСУ ФАКТОР-2 РЕЦЕПТОР ЭКСПРЕССИЯСЫНЫҢ АУРУДЫҢ ЖАСЫМЕН, ЖЫНЫСЫМЕН, ІСІКТІҢ ДИФФЕРЕНЦИАЦИЯЛЫҚ САТЫСЫ ЖӘНЕ ДӘРЕЖЕСІМЕН БАЙЛАНЫСЫ

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Өзектілігі: *Асқазанның қатерлі ісігі (АҚІ) – гетерогенді қатерлі ауру. Карциномаларда HER2 онкоген ретінде әрекет етеді, себебі геннің жоғары күшейтілуі жасуша мембранасындағы ақуыздың шамадан тыс экспрессиясын және кейіннен қатерлі жасуша үшін пайдалы қасиеттерді алуды тудырады. Жаңа және тиімді биомаркерлерді анықтау асқазан обырының диагностикасын жақсарту, асқазан обыры диагностикасының дәлдігін жақсарту, болжамды анықтау және патогенезді болжау, асқазан обыры бар науқастарды емдеудің жаңа және тиімді нұсқасын құру үшін қажет.*

Зерттеудің мақсаты: *асқазан обырындағы HER2 маркерінің экспрессиясын аурудың жасы, жынысы, ісік дифференциациясының сатысы және дәрежесі арасындағы байланысты бағалау.*

Әдістері мен материалдары: *Зерттеу дизайны салыстырмалы сипаттамалық зерттеу болып табылады. Зерттеуге 2021-2022 жылдар аралығында Марат Оспанов атындағы Батыс Қазақстан медицина университетінің медициналық орталығының патологоанатомиялық бөлімшесінен асқазан обырына операция жасау кезінде алынған асқазан обырының 0-IIIC сатысы бар 109 науқастың хирургиялық материалы қолданылды. Гистологиялық және иммуногистохимиялық зерттеулер Марат Оспанов атындағы БҚМУ гистология кафедрасының морфологиялық зертханасында жүргізілді. Алынған мәліметтер статистикалық өңдеуден өтті.*

Нәтижелері: *Осы зерттеуде GC-де оң Her2/neu экспрессиясының көрсеткіштері науқастың жасына (p=0,026) және жынысына (p=0,023) байланысты статистикалық түрде айтарлықтай ерекшеленді, бірақ локализацияға, ісіктің гистологиялық дифференциациясына және аурудың сатысына байланысты статистикалық айтарлықтай ерекшеленбеді.*

Қорытынды: *Төмен дифференцирленген асқазан обырында (50%) және аурудың II-III сатыларында Her2/neu оң экспрессиясының маңыздылығына тенденцияны ескере отырып, Her2/neu маркері мақсатты терапияны тағайындау кезінде алдын ала тестілеуді қажет ететін әлеуетті терапевтік мақсат ретінде қарастырылуы мүмкін.*

Түйінді сөздер: *асқазанның қатерлі ісігі, морфология, гистология, иммуногистохимия, Her2/neu.*

АННОТАЦИЯ

СВЯЗЬ ЭКСПРЕССИИ РЕЦЕПТОРА ЧЕЛОВЕЧЕСКОГО ЭПИДЕРМАЛЬНОГО ФАКТОРА РОСТА-2 ПРИ РАКЕ ЖЕЛУДКА С ВОЗРАСТОМ И ПОЛОМ ПАЦИЕНТА, СТАДИЕЙ И СТЕПЕНЬЮ ДИФФЕРЕНЦИРОВКИ ОПУХОЛИ

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Актуальность: *Рак желудка (РЖ) представляет собой гетерогенное злокачественное заболевание. При различных формах РЖ, например, карциноме, биомаркеры рецепторов эпидермального фактора роста человека Her2/neu выполняют роль онкогенного фактора, в основе которого лежит процесс высокой амплификации гена с переходом в злокачественную клетку. Сверхэкспрессия белка происходит на поверхности клеточной мембраны. В связи с этим необходимо расставить приоритеты по прогнозу, патогенезу и представить наиболее оптимальный по эффективности вариант лечения для пациентов с РЖ.*

Цель исследования *– оценить уровень экспрессии Her2/neu при раке желудка с учётом пола и возраста пациента, стадии заболевания и степени дифференцировки опухоли.*

Методы: *Нами было проведено сравнительное описательное исследование операционного материала, полученного от 109 пациентов с раком желудка со стадиями 0-IIIC после операций по поводу данного заболевания из патологоанатомического отделения НАО МЦ «ЗКМУ имени Марата Оспанова» в 2021-2022 гг. Различные гистологические и иммуногистохимические исследования проводили на кафедре гистологии морфологической лаборатории ЗКМУ им. Марата Оспанова. Полученные результаты обработаны различными методами статистической обработки.*

Результаты: *Настоящее исследование показало, что показатели положительной экспрессии Her2/neu при РЖ статистически значимо различаются в зависимости от возраста (p=0,026) и пола (p=0,023) пациента, но статистически не значимо различаются в зависимости от локализации, гистопатологической дифференцировки опухоли и стадии заболевания.*

Заключение: *Учитывая тенденцию к значимости положительной экспрессии Her2/neu при низкодифференцированном РЖ (50%) и II-III стадиях заболевания, маркер Her2/neu можно рассматривать как потенциальную терапевтическую мишень, требующую предварительного тестирования при назначении таргетной терапии.*

Ключевые слова: *рак желудка (РЖ), морфология, гистология, иммуногистохимия, Her2/neu.*

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NEEDLE-CATHETER JEJUNOSTOMY IN GASTRIC CANCER SURGERY

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ABSTRACT

Relevance: *The European Society for Parenteral and Enteral Nutrition recommends enteral feeding as a preferred route of administration of nutrients. Still, nasogastric intubation after operations on the digestive system is accompanied by discomfort in the stomach, an increase in the frequency of wound infection, insolvency of anastomotic sutures, pulmonary complications, and length of hospitalization.*

The study aimed to *assess the possibilities of catheter jejunostomy for postoperative enteral feeding of patients with gastric can-cer.*

Methods: *This study is based on clinical evaluation and surgical treatment results of 71 patients who received enteral nutrition following gastrectomy and gastric resection due to malignancy. Enteral nutrition was administered via a nasojejunal tube in 36 patients (control group) and through a percutaneous catheter enterostomy in 35 patients (experimental group). The principles of enter-al nutrition were standardized across both groups.*

Results: *The studies have shown that using various enteral nutrition products in the control and main groups affected patients' quality of life differently. During the entire follow-up period, the greatest discomfort in both groups was associated with transnasal probes. At the same time, the quality of life in the control group was the lowest. In the main group, during the entire follow-up peri-od, the effect of catheter enterostomies on patients' quality of life was minimal, while 14 (40%) patients did not experience any dis-comfort. This indicates that patients tolerate this method of providing enteral nutrition well. There were no requests to remove the enterostome or cases of self-removal during the entire observation period. In addition, no complications from either the abdominal cavity or the anterior abdominal wall were noted in the main group during the period of its functioning, as well as after its extrac-tion.*

Conclusion: *Catheter jejunostomy provides the possibility of reliable enteral nutrition for patients with gastric cancer after surgical treatment for a long time. The advantages of this treatment method are high safety and good patient tolerance.*

Keywords: *catheter, jejunostomy, gastric cancer, surgical treatment, enteral nutrition.*

Introduction: According to the recommendations of the European Society, the choice between parenteral and enteral nutrition comes down to the advantages of the enteral route of nutrient administration [1].

Enteral nutrition is the most physiological and appropriate. The entry of food compounds into the liver through the portal vein system promotes more physiological regulation of protein synthesis and metabolism in the liver and other internal organs. Some biochemical processes in the intestinal wall, such as transamination, do not occur with parenteral nutrition. Parenteral nutrition leads to an increase in the volume of circulating blood and, accordingly, an increase in the load on the heart, which is accompanied by additional energy expenditure.

Enteral nutrition provides the following clinical effects: 1) activation of motility and regeneration of the mucous membrane; 2) early activation of the absorption function of the lower intestine; 3) nutrient substrates activate intestinal hormones, which in turn support absorption at the level of various cells; 4) prevents excessive contamination of the A IZ with microbes; 5) is a preventive measure for acute erosive and ulcerative diseases; 6) stops the catabolic direction of metabolism; 7) helps improve immunity [2].

According to modern concepts, the intestine is not only responsible for digestion and absorption. The mucous membrane of the small and large intestines does not require nutrients. It has been proven that intraluminal administration of small amounts of food has a pronounced trophic effect on enterocytes, allowing them to maintain their functional activity. This activity ensures endocrine, immune, metabolic, and barrier functions, which are prerequisites for the patient's speedy recovery. Preclinical studies show that parenteral nutrition can cause atrophic damage to the intestinal mucosa. The study revealed a decrease in the thickness of the muscular layer of the mucosa and pronounced atrophy of the small intestine's villi after total parenteral nutrition compared with enteral nutrition [3].

Prolonged use of nasogastric tubes can cause significant discomfort in patients and is associated with the risk of perforation of the nose, throat, esophagus, stomach, and intestines [4]. The negative psychoemotional impact of transnasal intubation often leads to patients unconsciously removing the tube on their own, including during sleep. Rigid fixation of the tube to the wings of the nose using suture material leads to significant cosmetic defects of the face and is not recommended for wide use. A serious complication of a nasointestinal tube is the development of an acute ulcer of the stomach and duodenum, accompanied by severe bleeding. A foreign

body in the esophagus or oropharynx and the lack of a hermetic closure of the esophageal sphincter create favorable conditions for pathogenic microorganisms to migrate into the trachea and bronchi. Given the mentioned advantages of enteral nutrition, it is necessary to determine whether the method we propose – catheter jejunostomy – is the most physiologically effective. Ulcers and bleeding do not complicate catheter jejunostomy; it prevents food from entering the bronchi, preserves the intestine's anatomical and physiological state, and does not lead to villus atrophy. This is one of the most accurate methods, especially for patients after surgery for gastric cancer.

The study aimed to assess the possibilities of catheter jejunostomy for postoperative enteral feeding of patients with gastric cancer.

Materials and methods: The work is based on the results of the examination and surgical treatment of 71 patients who underwent enteral nutrition after gastrectomy and gastric resection for cancer. Of these, 49 (69%) were men, and 21 (31%) were women aged 37 to 77. Stages I and II a, b - 10 (14%), III - 61 (86%). In 6 (8.4%) patients, the first bile duct was located in the cardioesophageal region, in 12 (16.9%) - in the cardiac region of the stomach, in 30 (42.2%) - in the body of the stomach, in 23 (32.3%) - in the antral region. Gastrectomy with lymph node dissection (LND) was performed in 39 patients (54.5%), proximal gastrectomy with resection of the lower third of the esophagus using thoraco-laparotomy approach in combination with LND – in 7 patients (9.8%), proximal resection with LND – in 7 patients (9.8%), proximal resection with LND – in 8 patients (11.2%), distal resection with LND – in 17 patients (23.9%). In the control group (n=36), the patients received nutrients via a nasojejunal tube, and in the main group (n=35), a percutaneous catheter enterostomy was installed. The principles of enteral nutrition were the same in both groups.

Patients in the main and control groups were relatively comparable in gender, age, the underlying disease, and the type of surgical intervention (Table 1).

Table 1 – Distribution of patients by surgical methods performed

Operations	Control group (n=36)	Main group (n=35)	Total (n=71)
Gastrectomy	19 (52.7%)	20 (57.1%)	39 (54.5%)
Proximal gastrectomy	4 (11.1%)	4 (11.4%)	8 (11.2%)
Proximal gastrectomy performed by combined approach	4 (11.1%)	3 (8.5%)	7 (9.8%)
Distal gastrectomy	9 (25%)	8 (22.8%)	17 (23.9%)
Total	36 (100%)	35 (100%)	71 (100%)

After the main stage of the surgery, a 1.7 mm diameter catheter was inserted into the antimesenteric wall of the small intestine at a distance of 25-30 cm from the Treitz ligament. A jejunostomy was applied 30 cm from the intestinal anastomosis during gastric resection. For early enteral nutrition, a catheter jejunostomy was used 6 hours after the operation. The enteral infusion was gradually increased to 500 mL on Day 1 and 2 L on Day 10. Thus, oral food intake was completely excluded for up to 10 days. The catheter was removed on Day 14 after insertion, and no additional surgical intervention was required for its removal. After removing the fixing skin suture, the catheter was removed from the intestinal lumen, and the channel closed on its own on Day 1.

In the control group, a gastrointestinal tube was used for enteral nutrition. The distal part of the tube was passed through the duodenum as distally as possible to the initial loop of the small intestine or the interintestinal anastomosis through the gastrointestinal anastomosis.

Patients were treated and monitored in the intensive care unit in the early postoperative period. After their condition stabilized, they were transferred to surgical wards.

We used a visual analog scale to compare the impact of a nasogastric tube and catheter enterostomy on patients' quality of life. A score of 0 corresponded to no discomfort and a score of 5 to obvious suffering and a constant desire to remove the tube or enterostomy. Patients were examined on Days 1, 3, 5, and 7 after surgery once they had completed their resuscitation. When assessing the quality of life, patients in the control group described the degree of discomfort caused by a nasojejunal tube. In contrast, patients in the main group described the discomfort caused by a decompression tube and a catheter enterostomy.

Results: The study showed different effects of various enteral nutrition methods on patients' quality of life in the control and main groups (Figure 1). The difference between this study and a similar study conducted in 2018 is the larger number of patients included. In this regard, the obtained results have also changed significantly. The results showed that this method, i.e., catheter jejunostomy, is still considered the most effective for patients after gastrectomy [5].

Discussion: The greatest discomfort in both groups was associated with using transnasal tubes throughout the observation period. The control group had the lowest quality of life. Discomfort from the tube increased from 3.2 points on Day 1 after surgery to 4.3 points on Day 5. The nasojejunal tube significantly complicates nasal breathing and affects the receptors of the oropharynx's nasal passages, nasopharynx, and mucous membrane. In the main group, the maximum discomfort from the presence of the tube was recorded at 2.5 points on Day 3 after laparotomy.

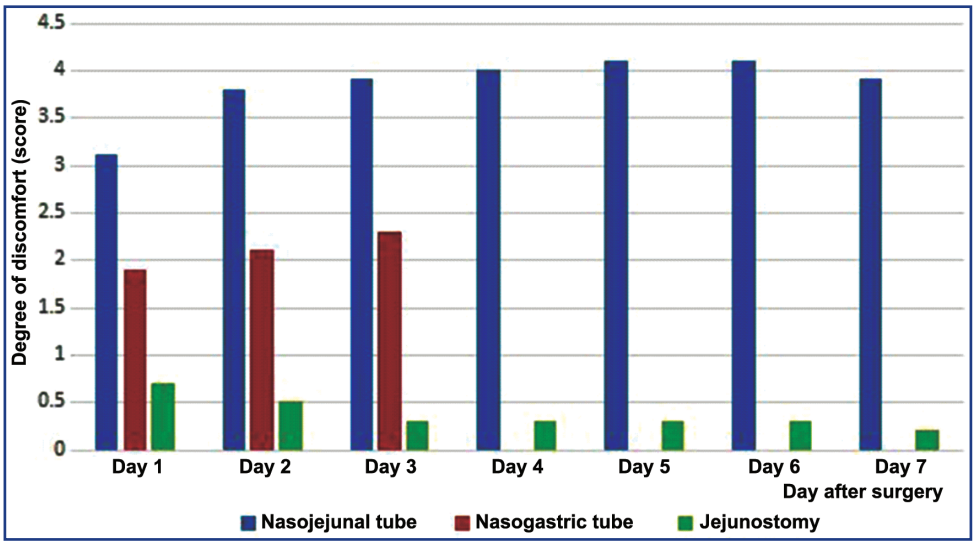

Figure 1 – Quality of life of patients after surgery

Figure 1 demonstrates an increasing negative psychoemotional impact of transnasal tubes with an increasing observation period. In the control group, 20 (55.5%) patients required tube removal on Day 3 after surgery and 27 (75%) on Day 5. Also, 9 (25%) patients couLND not tolerate the tube for 3-5 days after surgery, so they removed it themselves. In all cases, the motive for such behavior was discomfort, assessed on a 5-point numerical scale. In the main group, requests for tube removal were recorded in 3 of 14 patients (21.4%) on Day 3 after surgery, which coincided with the time of its removal for medical reasons.

In the main group, the impact of catheter enterostomy on patients' quality of life was minimal throughout the entire observation period: 14 (40%) patients did not report any discomfort. The presented indicators demonstrate the tolerability of providing enteral nutrition in patients. During the entire observation period, there were no requests for enterostomy removal and no cases of spontaneous removal. In addition, in the main group, there were no complications from the abdominal cavity and anterior abdominal wall during the jejunostomy operation and after its removal. According to the data presented in the article "Symptomatic surgical interventions for widespread gastric cancer," postoperative complications in such interventions are observed in 5-40% of cases, and postoperative mortality ranges from 4% to 32% [6]. These data emphasize the importance of choosing this nutrition method in the postoperative period, where catheter jejunostomy can significantly reduce the risk of complications and improve patient quality of life.

When assessing the effect of long-term transnasal tube placement on the risk of pneumonia, it was found that this type of postoperative complication was observed in 5 (13.8%) patients in the control group. The development of postoperative pneumonia is associated with impaired respiratory processes and mucus accumulation around the tube. In the main group, nosocomial pneumonia was detected only in 2 (5.7%) patients. The difference in pneumonia frequency between patients in the control and main groups was significant ($p < 0.05$). The data obtained demonstrate the undeniable advantages of catheter enterostomy compared to transnasal tubes regarding the frequency of pulmonary complications.

Conclusion: Thus, catheter jejunostomy provides patients with gastric cancer with the possibility of reliable enteral nutrition after surgical treatment for a long time. The method allows the restoration of peristalsis 2-3 days earlier. It improves the immediate results of surgical treatment for gastric cancer by eliminating protein-energy deficiency, normalizing intestinal structure and metabolism, preventing bacterial translocation, and dystrophic and atrophic changes in the intestinal mucosa. This treatment method's benefits include high safety and good patient tolerability.

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АННОТАЦИЯ

КАТЕТЕРНАЯ ЕЮНОСТОМИЯ ПРИ ХИРУРГИЧЕСКОМ ЛЕЧЕНИИ БОЛЬНЫХ РАКОМ ЖЕЛУДКА

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Актуальность: *Европейское общество парентерального и энтерального питания рекомендует энтеральное питание в качестве предпочтительного пути введения питательных веществ. Однако назогастральная интубация после операций на пищеварительной системе сопровождается дискомфортом в желудке, увеличением частоты раневой инфекции, несостоятельностью швов анастомоза, легочными осложнениями и длительностью госпитализации.*

Цель исследования *– изучение возможностей использования катетерной еюностомии для энтерального питания у больных с раком желудка в послеоперационном периоде.*

Методы: *Работа основана на результатах обследования и хирургического лечения 71 больных, которым проводилось энтеральное питание после гастрэктомии и резекции желудка по поводу рака. У 36 из них (контрольная группа) для введения нутриентов использовали назоеюнальный зонд, у 35 (основная) – через кожную катетерную энтеростому. Принципы проведения энтерального питания были едиными в обеих группах.*

Результаты. *Проведенные исследования показали, что в контрольной и основной группах использование различных средств энтерального питания по-разному влияло на качество жизни больных. За весь период наблюдения в обеих группах наибольший дискомфорт был сопряжен с трансназальными зондами. При этом в контрольной группе качество жизни было самым низким. В основной группе за весь период наблюдения влияние катетерных энтеростом на качество жизни пациентов было минимальным, при этом 14 (40%) больных не отметили какого-либо дискомфорта. Это свидетельствует о хорошей переносимости больными данного способа обеспечения энтерального питания. Запросов на удаление энтеростомы а также случаев ее самостоятельного удаления за весь период наблюдений зафиксировано не было. Кроме того, в основной группе в период функционирования еюностомы, а также после ее извлечения не было отмечено ни одного осложнения со стороны как брюшной полости, так и передней брюшной стенки.*

Заключение: *Катетерная еюностомия обеспечивает возможность надежного энтерального питания больных раком желудка после хирургического лечения в течение длительного времени. Преимуществами данного метода лечения служат высокая безопасность, хорошая переносимость его больными.*

Ключевые слова: *катетер, еюностомия, рак желудка, хирургическое лечение, энтеральное питание.*

АНДАТПА

АСҚАЗАННЫҢ ҚАТЕРЛІ ІСІГІН ХИРУРГИЯЛЫҚ ЖОЛМЕН ЕМДЕУ КЕЗІНДЕГІ КАТЕТЕРЛІК ЕЮНОСТОМИЯ

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Өзектілігі: *Еуропалық парентеральды және энтеральды тамақтану қоғамы энтеральды тамақтануды қоректік заттарды қабылдаудың қолайлы жолы ретінде ұсынады. Алайда, ұзақ мерзімді назоинтестиналдық зондтың болуы пациенттерде елеулі қолайсыздықты тудырады және мұрын, жұтқыншақ, өңеш, асқазан мен ішек ойылуларының пайда болу қаупі осымен тікелей байланысты.*

Зерттеу мақсаты *– операциядан кейінгі кезеңде асқазанның қатерлі ісігі бар науқастардың энтеральды тамақтануында катетерлік еюностомияны қолдану мүмкіндіктерін зерттеу болып табылады.*

Әдістері: *Жұмыс гастрэктомиядан кейін және қатерлі ісікке байланысты асқазан резекциясынан кейінгі энтеральды тамақтанудан өткен 71 науқасты тексеру және хирургиялық емдеу нәтижелеріне негізделген. Олардың 36-сында (бақылау тобы) қоректік заттарды енгізу үшін назоеюнальды түтік пайдаланылды, ал 35-інде (негізгі топ) – тері арқылы катетерлі энтеростомасы қолданылды. Энтеральды тамақтану принциптері екі топта да бірдей болды.*

Нәтижелері: *өткізген зерттеуімізге үңілсек, науқастардың өмір сапасына энтереальды тамақтану әдістері әрқалай әсерін көрсетті. Трансназальды зонд арқылы тамақтану барлық әдіс арасында ең ыңғайсыз болып шықты. Өмір сапасы*

төмендеген бақылау тобына қарағанда, катетерлік еюностома орнатылған негізгі топтың 14 (40%) науқасы ыңғайсыздық танытпады. Еюностоманы өздігімен алу, алуды өтіну жағдайлары болмады. Іш қабырғасында ешбір асқыну еюностома тұрған уақытта да, оны алып тастаған соң да болмады. Бұл еюностоманың іш қуысына еш өзгеріс әкелмей, алып тасталынған соң өзінен кейін айтарлықтай із қалдырмайтынын көрсетеді.

Қорытынды: *катетерлік еюностомия асқазан қатерлі ісігіне жасалған операциядан кейін физиологиялық тұрғыдан тамақтанудың тиімді әрі қолайлы әдісі болып табылады. Яғни, басқа әдістерге қарағанда қауіпісіз, науқастар үшін ыңғайлы болып келеді.*

Түйінді сөздер: *катетер, еюностомия, асқазан ісігі, хирургиялық емдеу, энтеральді тамақтану.*

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EVALUATION OF THE EFFICACY OF ANTI-CD38 ANTIBODIES IN THE TREATMENT OF MULTIPLE MYELOMA: RESULTS OF RETROSPECTIVE STUDY

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ABSTRACT

Relevance: *A breakthrough in managing multiple myeloma is associated with introducing monoclonal antibodies, significantly increasing overall response rates and improving progression-free survival. Combination regimens with monoclonal antibodies and immunomodulators demonstrate high efficacy even in patients resistant to previous lines of therapy.*

The study aimed to *evaluate the efficacy of anti-CD38 monoclonal antibodies (daratumumab) in patients with multiple myeloma after one or more prior therapy lines with other drugs.*

Methods: *A retrospective medical data analysis was conducted on 22 patients with refractory or relapsed MM who received daratumumab from February 2018 to November 2023. Patients received daratumumab either as monotherapy or in combination with other agents. The efficacy assessment was performed using the criteria of the International Myeloma Working Group (IMWG).*

Results: *The overall response rate to daratumumab treatment was 59.1%. The overall survival rate was 100% at two years and 95% by the end of the analysis period. Disease progression was observed in 22.7% of patients. The safety profile was acceptable, with mild to moderate side effects predominating, including thrombocytopenia, anemia, and neutropenia.*

Conclusion: *Daratumumab is an effective treatment for patients with refractory or relapsed MM who have undergone multiple prior lines of therapy. Treatment with daratumumab leads to significant improvements in clinical outcomes and progression-free survival. These data support the feasibility of using daratumumab in MM therapy and highlight the need for further study of its combination regimens and predictive factors for better therapeutic response.*

Keywords: *multiple myeloma, relapsed/refractory multiple myeloma, anti-CD38 antibodies, monoclonal antibodies, daratumumab, treatment efficacy.*

Introduction: Multiple myeloma (MM) is a neoplastic hematopoietic system disease characterized by uncontrolled proliferation of plasma cells in the bone marrow. The proliferation of monoclonal plasma cells in the bone marrow disrupts the normal process of hematopoiesis, leading to anemia. In addition, malignant plasma cells secrete monoclonal immunoglobulin, the so-called paraprotein or M-protein, and infiltrate other vital organs [1]. It should be noted that MM is the longest-diagnosed type of cancer in the world due to the various spectrum of clinical symptoms, in particular, back and bone pain, which often leads to late referral to oncologists and hematologists [2].

MM accounts for 1-2% of all oncological diseases and 17% of all oncohematological pathologies. On a global scale, over 180,000 cases and 121,000 deaths due to MM are reported annually among men and women of all ages [3]. The incidence in men is higher than in women, and several authors have noted ethnic and racial differences. For example, MM is twice as common in people of Aframerican origin [4-7]. According to the National Cancer Institute, MM's 5-year overall survival (OS) in 2013–2019 composed 59.8% [8].

The use of proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies (MAs), and new therapies has significantly improved progression-free survival and overall survival in patients with multiple myeloma over the past decades [1, 9]. One of the effective drugs for MM treatment is IG1kappa MA, which binds to CD38 glycoprotein [10]. CD38 induces cell adhesion and cytokine release and is highly expressed on the surface of myeloma cells, making it a target for MA IG1kappa.

One of the initial indications for MA use was daratumumab monotherapy in pre-treated patients with MM who had received several prior lines of therapy, including proteasome inhibitors and immunomodulators, as well as in patients with refractory to proteasome inhibitors and immunomodulators [11]. A retrospective analysis of 34 cases with primary and repeated use of MA and immunomodulators in patients previously treated with these drugs and refractory to them and in patients previously not treated with these drugs showed that the use of MA in combination with immunomodulators was effective not only in patients not taking these agents but also demonstrat-

ed a clinical response in a third of patients who received repeated treatment with these drugs [12]. The clinical trial data that studied the efficacy of anti-CD38 MA monotherapy showed an overall response rate (ORR) in 31% of cases and a median OS of 20.1 months [13]. Besides, according to the Phase 2 SIRIUS clinical trial, which assessed the efficacy of MA as a monotherapy, the ORR was 30.4%, and the mean OS was 20.5 months [14, 15].

Two phase 3 clinical trials (CASTOR and CANDOR) assessed the efficacy of MA in combination with proteasome inhibitors in patients with relapsed/refractory MM. The final analysis of OS in a 6-year follow-up of patients treated with daratumumab in the CASTOR study showed that OS was significantly higher in the group with IG1kappa MA, and the mean OS in this group composed 49.6 months, and in the control group was – 38.5 months [16]. According to the final analysis of the CANDOR study, the progression-free survival (PFS) in patients treated with IgG1k MA was 28.4 months after a 50-month follow-up, compared to a control group (15.8 months) [17].

In a similar POLLUX study using MA combined with immunomodulators, the 12-month PFS amounted to 64.8%, and the ORT composed 92.9% [18].

The results of the aforesaid studies on the use of CD38-directed MA in treating patients with MM have shown the efficacy of various treatment regimens. In this respect, further study of the efficacy of anti-CD38 MA in patients with refractory/relapsed MM is needed [11-18].

The study aimed to evaluate the efficacy of anti-CD38 monoclonal antibodies (daratumumab) in patients with multiple myeloma after one or more prior therapy lines with other drugs.

Materials and Methods: A retrospective analysis of medical data was carried out in 22 patients with MM registered with the City Clinical Hospital No. 7 in Almaty, with 1 or more previous lines of therapy, who received daratumumab in monotherapy and/or in combination with other agents in the period from February 2018 to November 2023.

The study included 9 men and 11 women. The average age of patients at enrollment was 62±11.9 years, and 50% were over 65 years old. The study group included 59% of women and 41% of men. The time from diagnosis to initiation of IG1kappa MA therapy ranged from 3 to 62 months, with a median of 30.3 months. Notably, 50% of patients received more than three lines of therapy before initiation of MA treatment, and all patients received proteasome inhibitors. The data are presented in Table 1.

Table 1 – Clinical characteristics and refractory status of patients enrolled in the study (n=22)

Indicator	Value, n (share, %)
Number of patients	22 (100)
Median age at study entry, year (range)	62 (38-87)
Age >65 years	11 (50)
Sex	
Men	9 (41)
Women	13 (59)
Time from diagnosis to the start of daratumumab therapy, months (range)	30.3 (3-62)
Average number of prior therapies (range)	3.3 (1-6)
>3 lines of prior therapy	11 (50)
Prior autologous hematopoietic stem cell transplantation	2 (9.1)
Prior proteasome inhibitor therapy	22 (100)
Prior therapy with immunomodulators	12 (54.4)

Treatment regimen: Within the frames of monotherapy, patients received daratumumab 16 mg/kg IV or 1800 mg SC once weekly at 1-8 weeks, once every 2 weeks at 9-24 weeks, and once every 4 weeks from week 25 onwards until progression or intolerance development.

In cases of combination therapy with other agents, the following dosages of drugs have been used:

Daratumumab – 16 mg/kg IV or 1800 mg SC once a week at 1-8 weeks, once every 2 weeks at 9-24 weeks, and once every 4 weeks from week 25 onwards until progression or until intolerance development.

Bortezomib – 1.3 mg/m^2 subcutaneously or intravenously, days 1,4,8,11 (cycles 1-8).

Lenalidomide – 25 mg orally, days 1-21.

Pomalidomide – 4 mg once daily orally, days 1-21.

Dexamethasone – 20 mg orally or intravenously, days 1,2,4,5,8,9,11,12 (cycles 1-8) when used with Bortezomib, or Dexamethasone 40 mg orally or intravenously when used with Lenalidomide/Pomalidomide [19].

In order to assess the response, the International Myeloma Working Group (IMWG) criteria have been used [20]. The Overall Response Rate (ORR) was obtained by patients achieving a strict complete response, a complete objective response, a very good partial objective response, a partial objective response, a minimal response, and stabilization of the process. The OS was defined as the time from registration to death for any reason. Progression-free survival (PFS) was defined as the time from initiation of treatment with IG1kappa MA to disease progression or death from any cause. The analysis of OS and PFS was carried out using the Kaplan-Meier method. The MedCalc Software, Belgium, was used for statistical analysis.

Results: According to our study, the ORR of patients with MM for treatment with daratumumab composed 59.1%. Of

these, 13.6% of patients achieved a complete objective response, 18.2% achieved a very good partial response, and 13.6% achieved a partial response. In 13.6% of patients, a minimal response was noted. However, 22.7% of patients experienced the disease progression, including patients who underwent autologous hematopoietic stem cell transplantation (auto-HSCT). The distribution of patients depending on the response to IG1kappa MA therapy is presented in Table 2.

Table 2 – Response rate to treatment with anti-CD 38 MA

Response to anti-CD 38 MA therapy	Number of patients	
	Abs.	%
Overall response rate	13	59.1
Strict full response	0	0
Complete objective response	3	13.6
Very good objective partial response	4	18.2
Partial objective response	3	13.6
Minimal response	3	13.6
Stabilization of the disease	2	9.1
Disease progression	5	22.7
Death	2	9.1
Overall survival (OS) rate		95.45
Progression-free survival		72.73

After two years of follow-up, the OS amounted to 100%; by the end of the follow-up period, it declined to 95% (Figure 1).

In patients with a history of auto-HSCT, the OS composed 100%, but 50% experienced the disease progression on the IG1kappa MA therapy after an average of 2 years of follow-up (Figure 2).

Figure 2 – Progression-free survival (PFS) of patients on daratumumab therapy (n=22).

The findings highlight the importance of daratumumab as an effective tool for managing refractory or relapsed forms of the disease. The high rates of ORR and PFS indicate this drug's potential to improve patients' long-term outcomes.

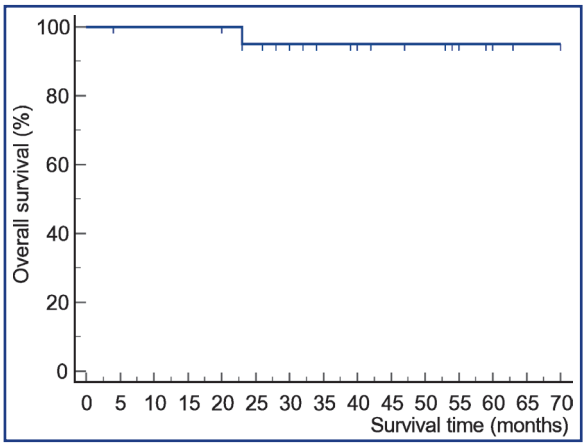

Figure 1 – Overall survival of patients with daratumumab therapy (n=22)

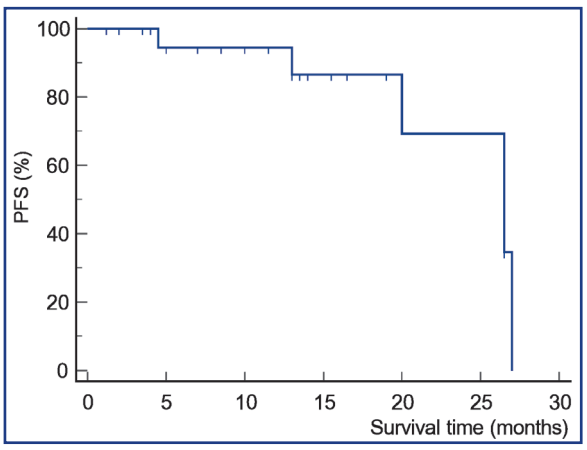

Рисунок 2

Safety profile: 72.8% of patients developed adverse reactions to daratumumab. According to Table 3, the most common side effects of anti-CD38 MA therapy were thrombocytopenia (9 patients) and anemia (7 patients). Neutropenia was observed in 5 patients, infectious complications in 2 patients, and severe neutropenia with fever in one patient required temporary treatment discontinuation. A reaction to the infusion was observed in 3 patients only at the first drug administration and did not require therapeutic intervention. This safety profile confirms that anti-CD 38 MA is a relatively safe drug, with a predominance of mild to moderate side effects. The incidence of serious adverse events was low, and most reactions did not require significant therapy changes.

Table 3 – Most common adverse events associated with Anti-CD38 MA treatment

Adverse Events Associated with Anti-CD38 MA Treatment	Total number of patients	
	Abs.	%
Neutropenia	5	22.7
Anemia	7	31.8
Thrombocytopenia	9	40.9
Pneumonia	1	4.5
Infection	2	9.1
Reaction to infusion	3	13.6

Discussion: The study results demonstrate that IG-1kappa MA is an effective treatment for patients with refractory or relapsed disease, including those who have received 3 or more lines of prior therapy, including a history of auto-HSCT [21,22]. The analysis of data from a retrospective study of 22 patients showed that the use of anti-CD38 MA both in monotherapy and in combination with other agents leads to significant improvements in clinical outcomes, including high rates of ORR and PFS. The MA safety profile was acceptable, predominating mild to moderate adverse reactions that did not require treatment discontinuation. The data of our study correlate with the world data on the therapy of refractory and relapsed MM using various treatment regimens with the inclusion of IG1kappa MA.

The studies of the MA efficacy in combination with proteasome inhibitors and immunomodulators in patients with newly diagnosed MM showed a significant improvement in PFS, complete response achievement, and a negative outcome of minimal residual disease in patients treated with daratumumab, compared to the control group [21-24]. The findings support the use of daratumumab in patients with refractory and relapsed forms of the disease and as a first-line therapy to improve clinical response and patient survival.

Conclusion: The efficacy of daratumumab in treating MM is currently beyond doubt. The use of anti-CD38 monoclonal drugs in first-line therapy has been shown to improve the OS and PFS. Numerous studies also support the potential for expanding indications, including regimens in combination with daratumumab. The analysis of the results of daratumumab use in combination regimens may provide additional evidence of its efficacy and safety, allowing for even wider use of this drug in clinical practice. Besides, further studies to identify factors that determine response to therapy and possible failures are noteworthy, which will facilitate the personalization of treatment and improvement of outcomes for patients with MM.

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АҢДАТПА

КӨПТІК МИЕЛОМАНЫ ЕМДЕУДЕ АНТИ-CD38 АНТИДЕНЕЛЕРІНІҢ ТИІМДІЛІГІН БАҒАЛАУ: РЕТРОСПЕКТИВТІК ЗЕРТТЕУДІҢ НӘТИЖЕЛЕРІ

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Өзектілігі: *Көптік миеломаны емдеудегі серпіліс моноклоналды антиденелерді қолданудың басталуымен байланысты, бұл жалпы жауап жиілігін едәуір арттырып, аурудың үдеуінсіз өмір сүру көрсеткіштерін жақсартады. Моноклоналды антиденелер мен иммуномодуляторларды біріктіріп қолдану, алдыңғы терапияның бірнеше жолдарына төзімді науқастарда да жоғары тиімділігін көрсетеді.*

Зерттеу мақсаты *– басқа препараттар кластарымен бір немесе бірнеше алдыңғы терапия жолдарынан өткен көптік миеломасы бар науқастарда анти-CD38 моноклоналды антиденесі (даратумумабты) қолдану тиімділігін зерттеу.*

Әдістері: *2018 жылдың ақпанынан 2023 жылдың қарашасына дейін даратумумаб алған рефрактерлі немесе рецидивті көптік миелома диагнозы қойылған 22 пациенттің медициналық деректеріне ретроспективті талдау жасалды. Науқастар даратумумабты монотерапия түрінде де, басқа агенттермен комбинацияда да қабылдады. Тиімділікті бағалау Миелома*

бойынша Халықаралық (IMWG) жұмыс тобының критерийлеріне сәйкес жүргізілді.

Нәтижелері: *Даратумумабпен емдеуге жалпы жауап жиілігі 59,1%-ды құрады. Екі жылдан кейінгі жалпы өмір сүру деңгейі 100%, талдау кезеңінің соңында – 95% болды. Аурудың үдеуі пациенттердің 22,7%-ында байқалды. Қауіпсіздік профилі қанағаттанарлық болды, негізгі жанама әсерлер – тромбоцитопения, анемия және нейтропения сияқты жеңіл және орташа ауырлықтағы асқынулар.*

Қорытынды: *Даратумумаб рефрактерлі немесе рецидивті көптік миелома диагнозы қойылған және бірнеше алдыңғы терапия жолдарынан өткен науқастарды емдеудің тиімді құралы болып табылады. Даратумумабпен емдеу клиникалық нәтижелерді және аурудың үдеуінсіз өмір сүруді айтарлықтай жақсартады. Бұл мәліметтер даратумумабты көптік миелома емінде қолданудың орындылығын және оның біріктірілген режимдерін әрі қарай зерттеу қажеттілігін қолдайды.*

Түйін сөздер: *көптік миелома, қайталанған/рефрактерлік көптік миелома, анти-CD38 антиденелері, моноклоналды антиденелер, даратумумаб, емдеудің тиімділігі.*

АННОТАЦИЯ

ОЦЕНКА ЭФФЕКТИВНОСТИ АНТИ-CD38 АНТИТЕЛ В ЛЕЧЕНИИ МНОЖЕСТВЕННОЙ МИЕЛОМЫ: РЕЗУЛЬТАТЫ РЕТРОСПЕКТИВНОГО ИССЛЕДОВАНИЯ

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Актуальность: *Прорыв в лечении множественной миеломы (ММ) связан с началом использования моноклональных антител, которые значительно повышают частоту общего ответа (ЧОО) и улучшают выживаемость без прогрессирования (ВБП). Комбинированные схемы с моноклональными антителами (МА) и иммуномодуляторами демонстрируют высокую эффективность у пациентов с ММ, в том числе и с рецидивирующей и рефрактерной ММ.*

Цель исследования *– изучение эффективности использования анти-CD38 моноклонального антитела у пациентов с множественной миеломой после одной или/и нескольких предшествующих линий терапии другими классами препаратов.*

Методы: *Проведен ретроспективный анализ медицинских данных 22 пациентов с рефрактерной или рецидивирующей формой ММ, получавших анти-CD 38 МА в период с февраля 2018 по ноябрь 2023 года. Пациенты получали препарат как в монотерапии, так и в комбинации с другими агентами. Оценка эффективности проводилась с использованием критериев Международной рабочей группы по миеломе (IMWG).*

Результаты: *ЧОО на лечение препаратом анти-CD 38 МА составила 59,1%. Общая выживаемость через два года составила 100%, к концу периода анализа – 95%. Прогрессирование заболевания наблюдалось у 22,7% пациентов. Профиль безопасности был допустимым, с преобладанием легких и умеренных побочных эффектов, включая тромбоцитопению, анемию и нейтропению.*

Заключение: *Препарат анти-CD 38 МА является эффективным средством для лечения пациентов с рефрактерной или рецидивирующей формой ММ, прошедших несколько линий предшествующей терапии. Лечение с использованием МА анти-CD -38 приводит к значительному улучшению клинических результатов и ВБП. Эти данные поддерживают целесообразность использования анти-CD 38 МА в терапии ММ и необходимость дальнейшего изучения его комбинированных режимов и факторов, предсказывающих лучший ответ на терапию.*

Ключевые слова: *множественная миелома, рецидивирующая/рефрактерная множественная миелома, анти-CD38 антитела, моноклональные антитела (МА), даратумумаб, эффективность лечения.*

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EPIDEMIOLOGICAL STATUS OF SOFT TISSUE SARCOMAS IN THE REPUBLIC OF KAZAKHSTAN IN 2013-2023

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ABSTRACT

Relevance: *Soft tissue sarcomas (STSs) are rare, aggressive malignant neoplasms that arise from mesenchymal tis-sues. They account for no more than 1% of all malignant tumors, can develop at any age, and are more common in mid-dle-aged and older people.*

The study aimed to *obtain a complete epidemiological picture of soft tissue sarcomas in the Republic of Kazakhstan for 11 years, including data analysis for 2023. It considered various parameters such as age, gender, ethnicity, region, and tumor type.*

Methods: *The presented study included all patients registered in the national cancer registry of Kazakhstan from 2013 to 2023, with a diagnosis of STS (ICD-10 code: C49). The number of STS cases is presented as absolute crude rates per 100,000 population. Standardized morbidity and mortality rates were calculated using the World standard.*

Results: *From 2013 to 2023, 4697 cases of STS were reported, with an average increase in incidence of 13%. The STS incidence was 2.4 cases per 100 thousand population. In terms of prevalence among other types of cancer, STSs ranked 19th in incidence and 18th in mortality and were not among the top 10 causes of mortality and morbidity. The incidence rate of STS for both sexes was 2.1 per 100 thousand population; mortality was 0.8 per 100 thousand popula-tion. Morbidity and mortality were higher among men compared to women by 30% and 35%, respectively. Peaks in the incidence of STS were observed in the age groups 55-64 years (23.6% of cases) and 65-74 years (24%). Mortality from STS was observed in the age groups 55-64 years (24.3% of cases) and 65-74 years (17.5%).*

Conclusion: *STSs are varied, and their diagnosis can be difficult in the early stages. The increasing incidence with age, especially in middle-aged people, emphasizes the importance of active prevention and early diagnosis in older peo-ple.*

Keywords: *epidemiology, morbidity, soft tissue sarcoma, mortality.*

Introduction: Soft tissue sarcomas (STSs) and extraosseous sarcomas are a group of rare, aggressive malignancies that arise from mesenchymal tissues, often presenting diagnostic and therapeutic challenges. STS can develop at any age but is most common in middle-aged and older people. In pediatric oncology, STSs account for 7-10% of all childhood cancer cases. The most common sites of their localization are the extremities (60%) and retroperitoneal space (15%). The average age at diagnosis is 54 years. The five-year relative survival rate for all stages of STS is 58%, and the overall five-year survival rate is about 50% [1].

From 1990 to 2021, the global incidence of soft tissue and extraosseous sarcomas increased from 54,631 to 96,201. The crude incidence rate increased from 1.02 to 1.22 per 100,000 population. From 1990 to 2021, there was an increase in the incidence and crude mortality rates of soft tissue and extraosseous sarcomas, while the age-standardized rate decreased. The incidence rate is higher in males compared to females. Compared with 1990, the incidence rate among older people increased in 2021, while the incidence rate among children under 5 years decreased, and little change was observed in other age groups. The mortality rate among children and older people decreased [1].

In recent years, the STS incidence has been steadily growing worldwide, with significant differences in incidence rates between regions [2]. The overall incidence rate in Japan was 3.4 per 100,000 from 2016 to 2019 [3]. According to epidemiological studies, STS overall incidence in adults ranged from 4.2 to 4.7 per 100,000 persons per year from 1995 to 2007 [4].

A retrospective registry study conducted by the National Institute for Epidemiology and Registry Initiatives in Switzerland between 1996 and 2015 found improvements in the 5-year comparative survival rate for soft tissue sarcoma, which increased from 56.4% in the period 1996–2001 to 61.6% in 2011–2015 due to advances in the treatment of STS. It is worth noting that despite the increase in the overall population, the number of deaths from STS has increased significantly [5].

In the United States, 26,758 cases of STS were reported between 1978 and 2001, with a higher incidence in males than females [6]. A study by the North American Association of Central Cancer Registries examined the incidence of STS among adolescents and young adults aged 15–29 years from 1995 to 2008 and found a 34% higher incidence in males than females [7]. The male-to-female ratio in Northern India was 1.73:1 [8]. In the Veneto region of Italy, STS incidence rates were higher among males across all age groups between 1990 and 2018, with a moderate upward trend over the past three decades in males, while the incidence of STS among females remained stable. These findings may be related to environmental toxicants and occupational exposures, mainly involving men. In addition, the locations and subtypes of STS differ by gender. Retroperitoneal STS is more common in women, whereas men are more likely to develop tumors in the extremities, head, and neck [12]. Undifferentiated sarcomas and liposarcomas are more common in men, while leiomyosarcomas, especially uterine leiomyosarcomas, are most common in women [9].

In 2020, there were 13,130 cases of soft tissue cancer (STC) in the United States. The 5-year survival rate for STC patients was approximately 15%, with a median survival of 8 to 16 months. The most common sarcomas in adults are undifferentiated pleomorphic sarcoma, liposarcoma, and leiomyosarcoma. Distant metastases are most commonly seen in the lungs (43%), liver (14%), and bones (13%) [1].

In Europe, the incidence of sarcoma is 4-5 per 100,000 people per year. STSs account for about 1% of all malignant tumors in adults and up to 15% of malignant tumors in children aged 0-4 years [3].

In France, approximately 4,000 new STS cases are diagnosed annually, of which 23% are localized in the abdomen and pelvis [10].

From 2013 to 2017, 19,717 patients with STS were diagnosed in England (3943 patients per year), representing approximately 0.8% of malignancies. The most common diagnoses were gastrointestinal stromal tumors (20.2%), leiomyosarcoma (13.3%), and undifferentiated sarcoma (12.7%) [11].

The study aimed to obtain a complete epidemiological picture of soft tissue sarcomas in the Republic of Kazakhstan for 11 years, including data analysis for 2023. It considered various parameters such as age, gender, ethnicity, region, and tumor type.

Materials and methods: The presented study included all patients registered in the national cancer registry of Kazakhstan from 2013 to 2023 with a diagnosis of "Soft tissue sarcoma" (ICD-10 code: C49). Information in the cancer registry reflects demographic data, disease stage, histological type of tumor, treatment methods, and survival data throughout the country. Demographic variables included gender, age, and region of residence [12-18]. The number of STS cases is presented as absolute and crude indicators per 100,000 population. Standardized incidence and mortality rates are calculated using the world standard (World) and are given as absolute values. MS Excel 2013-2023 was used to visually display the calculated indicators [12-18].

Results: *Dynamics of incidence of soft tissue sarcomas in the Republic of Kazakhstan (RK) from 2013 to 2023.*

From 2013 to 2023, 4,697 cases of STS were registered, with an average increase in incidence of 13%. High incidence rates were recorded in 2015 (475 cases) and 2023 (473 cases). A decline in incidence was noted in 2017 and 2020, but since 2021, a stable incidence of more than 400 cases per year has been observed.

The mortality rate from 2013 to 2017 was high and varied from 188 to 200 cases. However, since 2018, mortality has decreased consistently from 177 to 138 cases in 2022. In 2023, there was an increase in mortality to 156, although 22% lower than the 2013 mortality, despite the increase in incidence in 2023 (Figure 1).

Oncological morbidity structure. In 2023, 37,038 new malignant neoplasms (MN) cases were registered in the Republic of Kazakhstan. Of these, 473 cases are soft tissue malignancies, which is 0.8% of the total number and ranks 19th in prevalence among other types of cancer. The STS incidence was 2.4 cases per 100 thousand population (Figure 2).

Statistics of incidence by gender and age groups. STS standardized incidence in both sexes was 2.1 per 100 thousand. STS incidence was higher in men – 2.4 per 100 thousand, compared to 1.8 per 100 thousand women.

STS peak incidence was observed at 55-64 years (23.6% of cases) and 65-74 years (24%). In the age groups of 35-44 years and 45-54 years, the incidence was 12.9% and 12.3%, respectively. The incidence among men exceeds the indicators among women in most groups and amounts to 30%. The lowest incidence is observed in the younger age categories (0-19 years) and the older group (85 years and older). (Figure 3).

Statistics of incidence by ethnicity. Statistics of STS incidence in women by ethnicity in 2023 were as follows: Kazakhs – 126 cases, Russians – 76 cases, other nations – 25 cases, Ukrainians – 9 cases. Among men, by ethnicity in 2023: Kazakhs – 134 cases, Russians – 67 cases, other nations – 29 cases, Ukrainians – 6 cases.

Thus, the highest STS incidence was observed in Kazakhs in both sexes (Figures 4, 5).

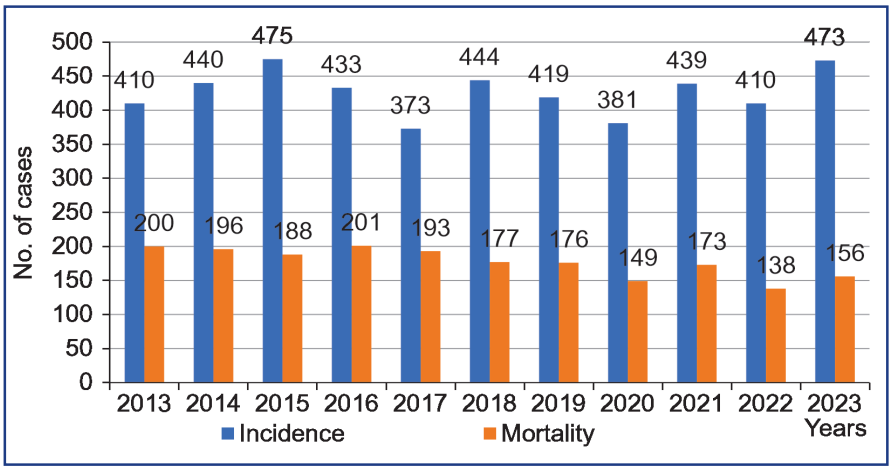

Figure 1 – Incidence and mortality rates from soft tissue sarcomas in the Republic of Kazakhstan 2013-2023 (absolute number of cases)

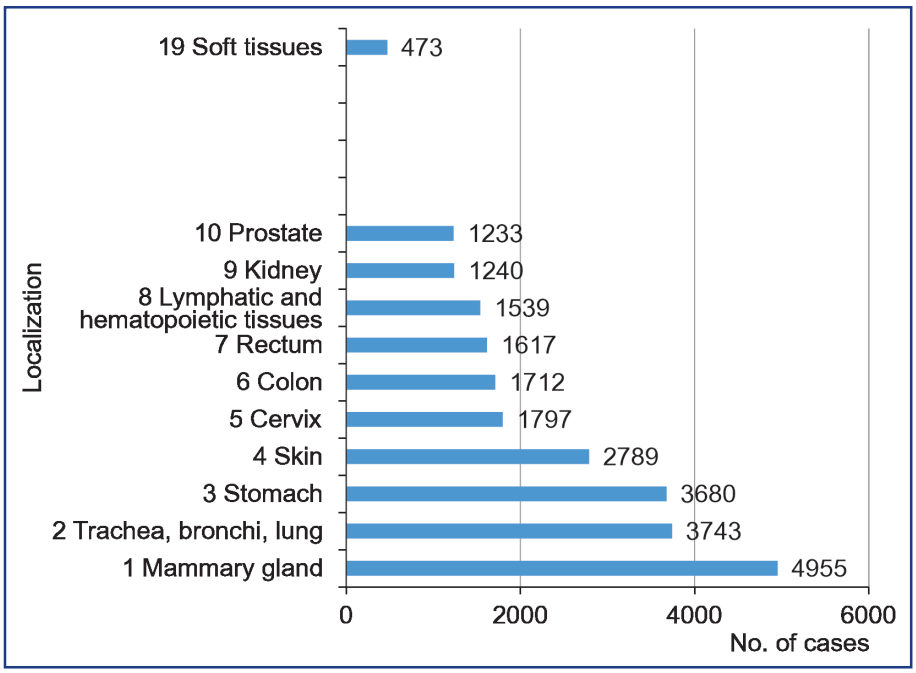

Figure 2 – Structure of cancer incidence in the Republic of Kazakhstan, 2023 (absolute number of cases)

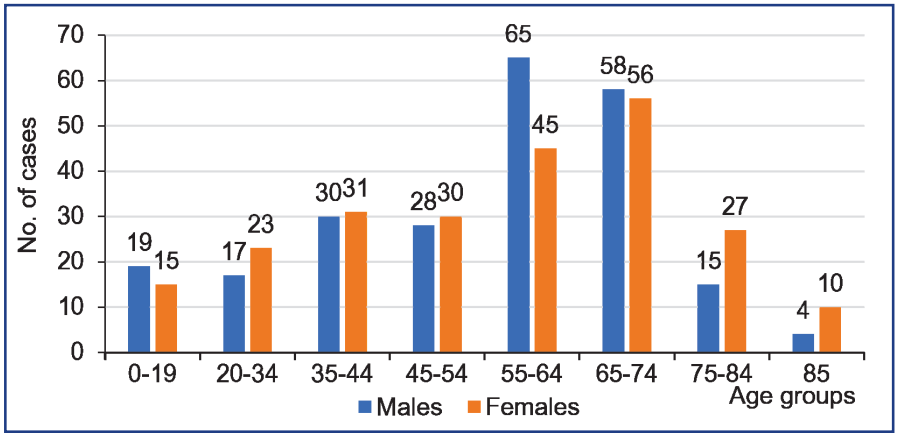

Figure 3 – Incidence rates of soft tissue sarcomas in the Republic of Kazakhstan, by gender and age groups, 2023 (absolute number of cases)

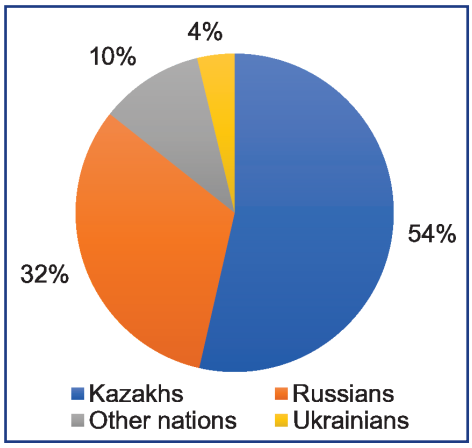

Figure 4 – Incidence of soft tissue sarcomas among women in the Republic of Kazakhstan, broken down by nationality, 2023 (% of cases)

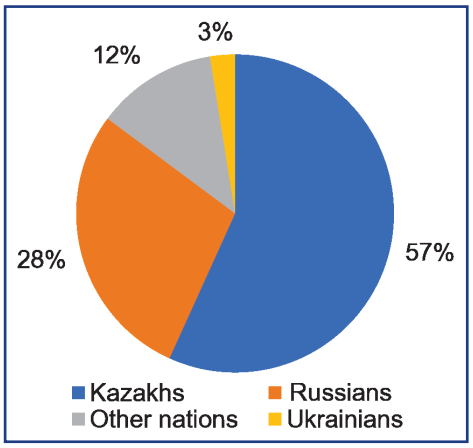

Figure 5 – Incidence of soft tissue sarcomas among men in the Republic of Kazakhstan, broken down by nationality, 2023 (% of cases)

Statistics of incidence by stages. The largest number of cases of STS were detected at stages II-III, which is 62%, at stage I – 23%, and at stage IV - 10%, which indicates the difficulty of STS early diagnosis.

Statistics of incidence by localization. STSs most often affect the soft tissues of the lower extremities (41%) and upper extremities (17%), as well as the head, face and neck (14.6%). 27.4% of sarcomas are located in other localizations (Figure 7).

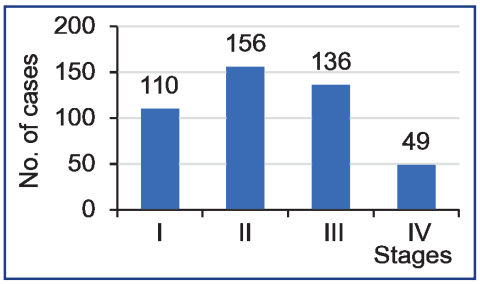

Figure 6 – Incidence of soft tissue sarcomas in the Republic of Kazakhstan, broken down by stages, 2023 (absolute number of cases)

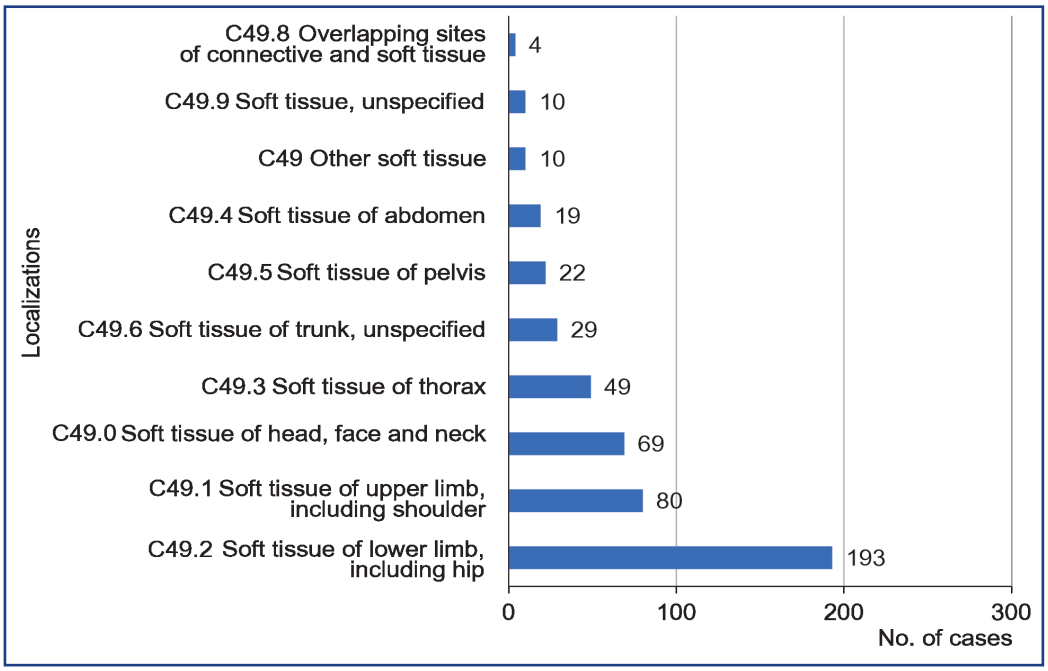

Figure 7 – Incidence of soft tissue sarcomas in the Republic of Kazakhstan, broken down by localization according to ICD 10, 2023 (absolute number of cases)

Statistics of incidence by histological type. By STC histotype, fibrosarcoma (25.6%), liposarcoma (20.6%) are most common, synovial sarcoma (11.8%), fibrous histiocytoma (10.6%). The remaining histological types account for 31.4% of the total number of cases of STS (Figure 8).

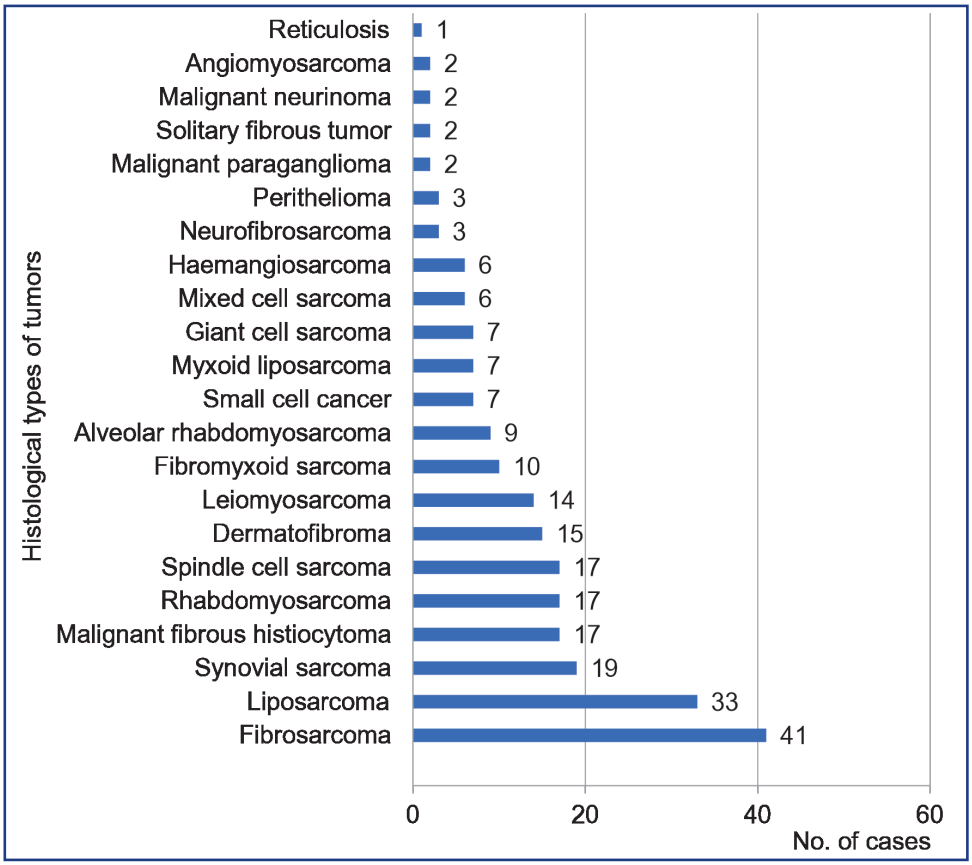

Figure 8 – Incidence of soft tissue sarcomas in the Republic of Kazakhstan, broken down by histological type according to ICD 10, 2023 (absolute number of cases)

Morbidity statistics by region. In the Republic of Kazakhstan in 2023, a high incidence rate of STS was observed in the city of Almaty (11.7%) of the total number of cases, Karaganda region (8%) and East Kazakhstan region (8%). A high rate in the city of Almaty indicates a high population density, the presence of an oncology center, and the potential for a more efficient early diagnosis and treatment system (Figure 9).

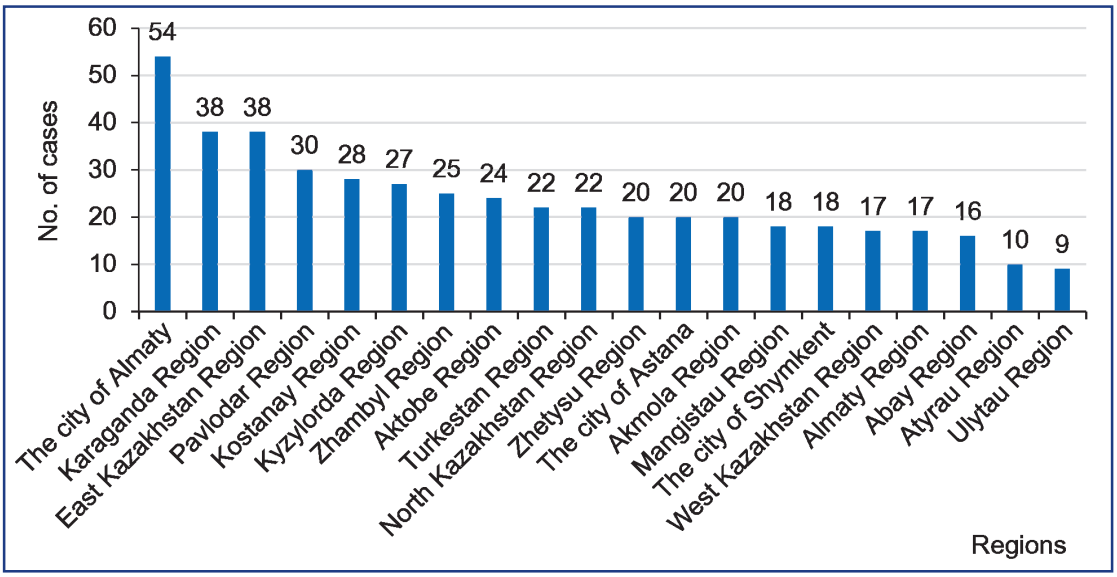

Figure 9 – Incidence of soft tissue sarcomas in the Republic of Kazakhstan, broken down by region, 2023 (absolute number of cases)

Mortality statistics by gender and age groups. STS standardized mortality rate in both sexes was 0.8 per 100,000 population. The peaks in STS mortality were observed in the age groups of 55-64 years (24.3% of cases) and 65-74 years (17.5%). In the age groups of 45-54 years and 75-84 years, mortality was 11% and 13%, respectively. Mortality rates were higher in men in most age groups and amounted to 35%. In the age groups of 45-54 years and older people and senile groups of 65-74 years and 75-84 years, the mortality was higher among women. The lowest mortality was observed in junior and young age groups (0-19 and 20-34 years) (Figure 10).

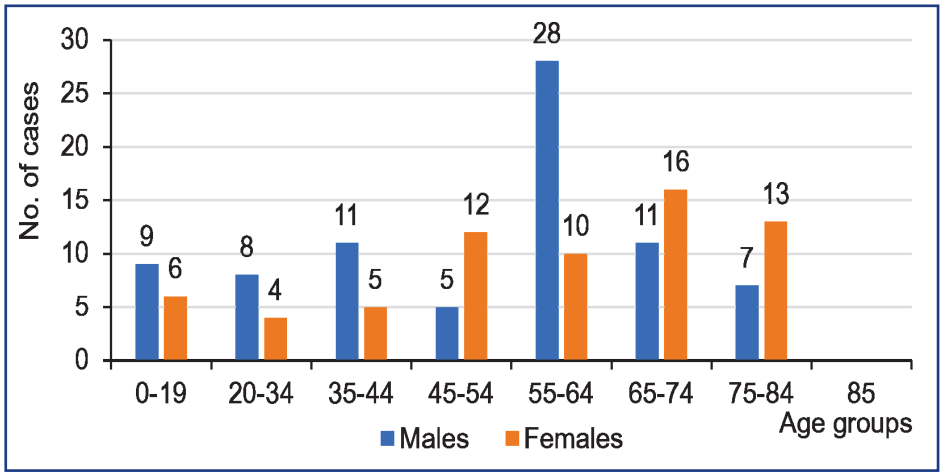

Figure 10 – Mortality rates from soft tissue sarcomas in the Republic of Kazakhstan, broken down by gender and age groups, 2023 (absolute number of cases)

In 2023, in the structure of deaths from malignant neoplasms by localization, STSs ranked 18th in mortality (156 cases). They were not among the top 10 causes of death from malignant neoplasms in Kazakhstan (Figure 11).

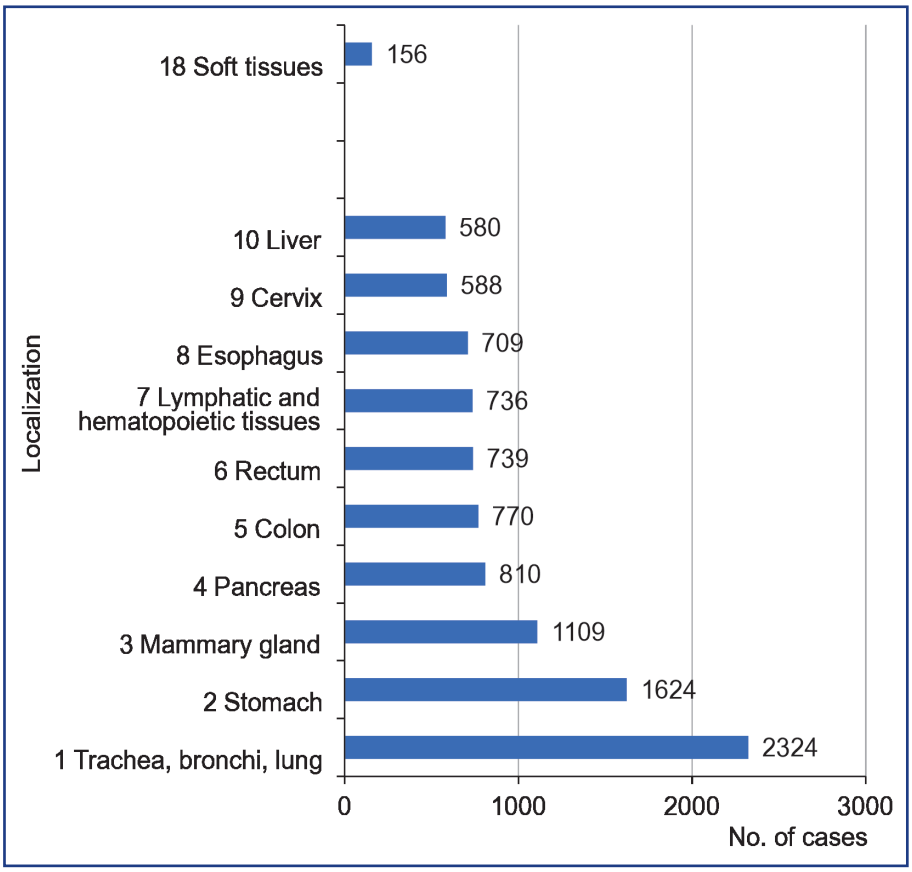

Figure 11 – Structure of mortality from malignant neoplasms in the Republic of Kazakhstan, broken down by localization, 2023 (absolute number of cases)

Mortality statistics by region. In the Republic of Kazakhstan in 2023, high mortality rates from STS were observed in the Zhambyl region (3.3% each), as well as in the Abay region and Almaty city. High rates in the Zhambyl and Abay regions may be due to the level of diagnosis, which leads to late detection of sarcomas, which worsens the prognosis (Figure 12).

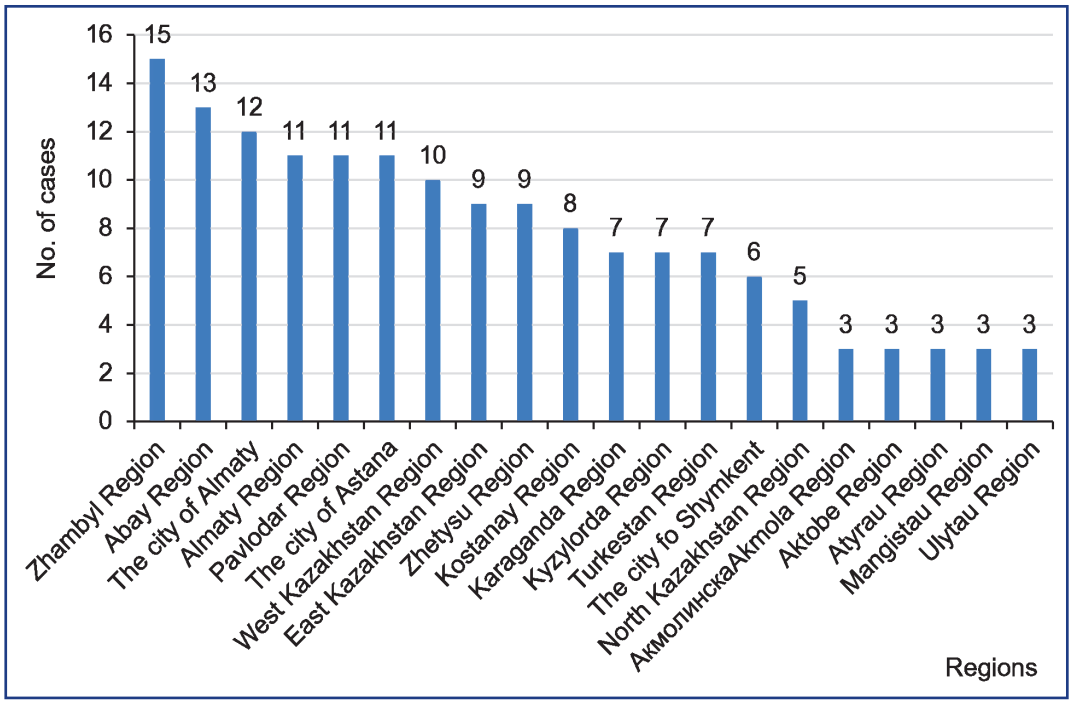

Figure 12 – Mortality from soft tissue sarcomas in the Republic of Kazakhstan, broken down by region, 2023 (absolute number of cases)

Discussion:

Despite the overall increase in STS incidence, there is a trend toward a gradual decrease in mortality. This may be due to improved treatment methods, which contribute to increased patient survival and higher awareness among physicians about sarcoma symptoms and modern diagnostic methods.

STS incidence was 2.4 cases per 100,000 population, which confirms that these tumors are a relatively rare type of malignancy. Although the focus is often on more common cancers, it is important not to forget the need for a specialized approach to rare cancers.

The increase in incidence with age, especially among the 55-74 age group, highlights the importance of active prevention and early diagnosis among older people. It is also worth noting that men are more likely to become ill and die in most age categories.

A high incidence in the city of Almaty could be due to the presence of a specialized center for treating bones and soft tissues at KazIOR, which facilitates accurate diagnosis and successful treatment of diseases.

STSs are diverse, and their diagnosis is challenging, especially in the early stages. Therefore, a multidisciplinary approach is essential, which includes teamwork between clinicians, pathologists, and radiologists.

Conclusion: Thus, from 2013 to 2023, 4697 STS cases were registered in the Republic of Kazakhstan. The incidence shows an average increase of 13%, with peaks in 2015 and 2023. At the same time, the mortality rate was high in the first years but gradually decreased since 2018. However, in 2023, the number of deaths increased, although compared to 2013, the mortality rate is still 22% lower.

In 2023, 37,038 new cases of malignant neoplasms were registered in the country, of which 473 cases were in soft tissues, which is only 0.8% of the total. At the same time, there is a high incidence in men (2.4 cases per 100 thousand population) compared to women (1.8 cases per 100 thousand). The largest number of cases was registered in the age groups of 55-64 and 65-74 years.

By ethnicity, the highest incidence is observed among Kazakhs, both men and women. It is also worth noting that 62% of cases are detected at stages II and III of the disease, which indicates the difficulties of diagnosis at early stages.

As for localization, sarcomas most often affect the soft tissues of the lower extremities, upper extremities, and head areas. The highest incidence was recorded by region in the Almaty, Karaganda, and East Kazakhstan regions.

The mortality rate from sarcomas is 0.8 per 100 thousand population, with the highest rates in the age groups

of 55-64 and 65-74 years. At the same time, mortality among men is higher than among women. In 2023, mortality from sarcomas was 156 cases, with high rates in the Zhambyl and Abay regions.

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АҢДАТПА

2013-2023 ЖЫЛДАРҒА АРНАЛҒАН ҚАЗАҚСТАН РРЕСПУБЛИКАСЫНДАҒЫ ЖҰМСАҚ ТІНДЕР САРКОМАЛАРЫНЫҢ ЭПИДЕМИОЛОГИЯЛЫҚ ЖАҒДАЙЫ

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Өзектілігі: *Жұмсақ тіндердің саркомасы – мезенхималық тіндерден пайда болатын, барлық қатерлі ісіктердің 1%-дан аспайтын, кез келген жаста дами алатын, бірақ орта және егде жастағы адамдарда жиі кездесетін сирек кездесетін агрессивті қатерлі ісіктер тобы.*

Зерттеудің мақсаты *– жасы, жынысы, ұлты, аймағы және ісік түрі сияқты әртүрлі параметрлерді ескере отырып, 2023 жылға арналған деректерді талдауды қоса алғанда, Қазақстан Республикасында 11 жыл ішінде жұмсақ тіндер саркомасының толық эпидемиологиялық бейнесін алу.*

Әдістері: *Ұсынылған зерттеуге жұмсақ тіндердің саркомасы диагнозымен (ICD-10 коды: C49) 2013-2023 жылдар аралығында Қазақстанның ұлттық онкологиялық реестрінде тіркелген барлық пациенттер қамтылды. Жұмсақ тіндер саркомасы жағдайларының саны 100 000 халыққа шаққанда абсолютті өрескел көрсеткіштер ретінде берілген. Стандартталған аурушаңдық пен өлім-жітім көрсеткіштері дүниежүзілік стандартты қолдану арқылы есептелді (World).*

Нәтижелері: *2013 жылдан 2023 жылға дейін жұмсақ тіндердің саркомасының 4697 жағдайы тіркелді, аурушаңдықтың орташа өсімі 13% құрайды. Жұмсақ тіндердің саркомасымен сырқаттанушылық 100 мың тұрғынға шаққанда 2,4 жағдайды құрады. Қатерлі ісіктің басқа түрлерінің арасында таралуы бойынша аурушаңдық 19-шы орында, ал өлім-жітім 18-ші орында және өлім мен сырқаттанушылықтың алғашқы 10 себебінің қатарына кірмейді. Екі жыныс үшін де СМТ-мен сырқаттанушылық көрсеткіші 100 мың халыққа шаққанда 2,1, өлім-жітім 100 мың халыққа 0,8 құрайды. Ерлер арасында аурушаңдық пен өлім-жітім әйелдермен салыстырғанда сәйкесінше 30% және 35% жоғары. ЖТҚ-мен сырқаттанушылықтың шыңы 55-64 жас (23,6% жағдайлар) және 65-74 жас (24%) жас топтарында байқалды. СТС-дан болатын өлім 55-64 жас (24,3% жағдайлар) және 65-74 жас (17,5%) жас топтарында байқалды.*

Қорытынды: *SMT әртүрлі және олардың диагнозы ерте кезеңде белгілі бір қиындықтарды тудырады. Жас ұлғайған сайын, әсіресе орта жастағы адамдарда аурушаңдықтың артуы егде жастағы тұрғындарда белсенді профилактика мен ерте диагностиканың маңыздылығын көрсетеді.*

Түйінді сөздер: *эпидемиология, аурушаңдық, жұмсақ тіндердің саркомасы, өлім-жітім.*

АННОТАЦИЯ

ЭПИДЕМИОЛОГИЧЕСКОЕ СОСТОЯНИЕ ПО САРКОМАМ МЯГКИХ ТКАНЕЙ В РЕСПУБЛИКЕ КАЗАХСТАН ЗА 2013-2023 годы

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Актуальность: *Саркомы мягких тканей – это группа редких, агрессивных злокачественных новообразований, которые возникают из мезенхимальных тканей, составляют не более 1% всех злокачественных опухолей, могут развиваться в любом возрасте, но чаще встречаются у людей среднего и пожилого возраста.*

Цель исследования *– получение полной эпидемиологической картины сарком мягких тканей в РК за 11 лет, включая анализ данных за 2023 год с учетом различных параметров, таких как возраст, пол, этническая принадлежность, регион и тип опухоли.*

Методы: *В представленное исследовании были включены все пациенты, зарегистрированные в национальном канцер-регистре Казахстана с 2013 по 2023 гг. с диагнозом «Саркома мягких тканей» (код ICD-10:C49). Количество случаев сарком*

мягких тканей представлено в виде абсолютных грубых показателей на 100 000 населения. Стандартизованные показатели заболеваемости и смертности рассчитаны с применением мирового стандарта (World) .

Результаты: *С 2013 по 2023 годы было зарегистрировано 4697 случаев сарком мягких тканей, средний прирост заболеваемости составил 13%. Заболеваемость саркомами мягких тканей составила 2,4 случая на 100 тысяч населения. По распространенности среди других видов рака заболеваемость занимает 19-е место, а смертность – 18-е место и не входит в топ – 10 причин смертности и заболеваемости. Показатель заболеваемости СМТ для обоих полов составляет 2,1 на 100 тысяч населения, смертность составляет 0,8 на 100 тысяч населения. Заболеваемость и смертность выше среди мужчин по сравнению с женщинами на 30% и 35%, соответственно. Пики заболеваемости СМТ наблюдались в возрастных группах 55-64 лет (23,6% случаев) и 65-74 лет (24%). Смертность от СМТ наблюдалась в возрастных группах 55-64 лет (24,3% случаев) и 65-74 лет (17,5%).*

Заключение: *СМТ разнообразны, их диагностика вызывает определённые сложности на ранних стадиях. Увеличение заболеваемости с возрастом, особенно у людей среднего возраста, подчеркивает важность активной профилактики и ранней диагностики среди пожилого населения.*

Ключевые слова: *эпидемиология, заболеваемость, саркома мягких тканей, смертность.*

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EFFICACY OF ERYTHROPOIETIN IN THE CORRECTION OF ANEMIA IN ONCOLOGY PATIENTS UNDERGOING CHEMOTHERAPY

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ABSTRACT

Relevance: *Anemia is a common complication in oncology patients, reducing their quality of life and potentially decreasing the effectiveness of antitumor therapy. Its prevalence among patients with solid tumors reaches 40%, and during chemotherapy, it increases to 54%. The deterioration in patients' condition is associated with chemotherapy-induced myelosuppression, making anemia correction a crucial task. The primary pharmacological method for correction is using erythropoietins, which stimulate the proliferation of erythroid progenitor cells.*

The study aimed to *evaluate the effectiveness and safety of erythropoietin in correcting anemia in oncology patients receiving chemotherapy, focusing on improving treatment outcomes by correcting hematological parameters in real clinical practice.*

Methods: *This prospective, non-interventional study included 133 patients from two clinical centers in Kazakhstan. Inclusion criteria: age ≥18 years, histologically confirmed solid tumor, anemia (Hb ≤100 g/L), and ongoing chemotherapy. The sample included 100 (75.2%) women and 33 (24.8%) men, with a median age of 60 years (52.0-67.5). The drug was administered 3 to 5 times in 78.2% of patients and 1 to 2 times in 21.8%. Statistical analysis was performed using the Friedman and Wilcoxon criteria, with a significance level of $p<0.05$.*

Results: *Data from 133 patients were analyzed. An increase in hemoglobin and erythrocyte levels was observed in 65.4-78.2% of patients. In the first and third months, hemoglobin levels increased by 0.6 g/L ($p<0.001$), and erythrocyte levels increased by 0.2-0.3×10¹²/L ($p<0.001$). 33.1% of patients received the drug five or more times. No serious adverse events were recorded.*

Conclusion: *Erythropoietin demonstrated a statistically significant improvement in clinical parameters, confirming its effectiveness and safety in correcting anemia in oncology patients receiving chemotherapy. This contributes to an improved quality of life and better treatment outcomes.*

Keywords: *anemia, oncology, chemotherapy, erythropoietin, erythropoiesis, anemia correction, biosimilar, solid tumors.*

Introduction: Anemia associated with chronic diseases occurs in 40% of cancer patients with solid tumors. The incidence of anemia during chemotherapy reaches 54%, with 30% of cases being mild, 9% moderate, and 1% severe. Anemia is most often observed in lung cancer (71%) and tumors of the female reproductive system (65%) [1, 2].

Chemotherapy may worsen anemia by decreasing hemoglobin levels and worsening the general condition of patients. In this context, the importance of anemia correction cannot be underestimated since it affects patients' quality of life and can also reduce the effectiveness of antitumor therapy [3]. Erythropoietins stimulate the proliferation of the erythroid hematopoietic lineage in the bone marrow. These drugs are actively used to correct anemia in cancer patients. Erythropoietin has been approved for clinical use and has shown its effectiveness in increasing hemoglobin levels and reducing the need for blood transfusions in patients receiving chemotherapy. However, despite its widespread use, questions remain about optimizing the administration regimen, efficacy, and safety profile. In this regard, there was a need to conduct this study in real clinical practice to assess the efficacy and safety of erythropoietin in cancer patients receiving chemotherapy.

The study aimed to evaluate the efficacy and safety of erythropoietin in the correction of anemia in cancer patients receiving chemotherapy, focusing on improving treatment outcomes by correcting hematological parameters in real clinical practice.

Objectives of the study: to analyze the drug's effect on hemoglobin levels, the frequency of blood transfusions, and the general condition of patients, as well as to identify possible side effects when using it in real clinical practice.

Materials and methods: The study was prospective, non-interventional, and conducted in two clinical centers in Kazakhstan. The study included and analyzed data from 133 patients. The main inclusion criteria were age 18 years, verified diagnosis of solid cancer, laboratory-confirmed anemia (hemoglobin level ≤100 g/L), and ongoing chemotherapy. The study patients included individuals of both sexes, with a three-fold predominance of females: 100 women (75.2%) and 33 men (24.8%). The average age of

patients was 60 years (range 52.0-67.5). Most study participants (57.1%) had a normal body mass index. The predominant tumor localizations included gynecological tumors – 40 patients (30.1%), tumors of the gastrointestinal tract – 38 patients (28.6%), breast cancer – 22 patients (16.5%), and other localizations – 33 patients (24.8%) (Table 1).

Table 1 – Clinical and demographic characteristics of patients

Indicator	n (%)
Floor	
Men	33 (24.8%)
Women	100 (75.2%)
Age (Median (Q_1-Q_3))	60 (52.0-67.5)
Body mass index	
16-18.5	2 (1.5%)
18.5-25	76 (57.1%)
25-30	41 (30.8%)
30-35	11 (8.3%)
35-40	3 (2.3%)
Tumor localization	
Hematological	3 (2.3%)
Gynecological	40 (30.1%)
Heads and necks	7 (5.3%)
Gastrointestinal tract	38 (28.6%)
Leather	2 (1.5%)
Lungs	8 (6.0%)
Breast	22 (16.5%)
Urogenital system	9 (6.8%)
The locomotor system	4 (3.0%)
Total	133 (100%)

Patients received erythropoietin 40,000 IU/ml for 6 months before inclusion in the study. The total number of drug administrations ranged from 3 to 5 in 78.2% of patients. The most common chemotherapeutic agents were Cisplatin, Carboplatin, and Paclitaxel. These drugs were used for chemotherapy in 74-90 patients (55.6-67.6%).

The study analyzed changes in hemoglobin levels, red blood cell (RBC) count, and the data on side effects. The drug's efficacy was assessed based on changes in hemoglobin levels and RBC count, and safety was assessed based on monitoring adverse events.

Statistical analysis used the Friedman and Wilcoxon criteria to compare laboratory data before and after drug administration. The Kruskal-Wallis criterion was used to compare the blood parameters, considering the number of erythropoietin administrations and chemotherapy courses. The results were considered statistically significant at $p<0.05$.

Results: Data from 133 patients with solid tumors who received erythropoietin for 6 months were analyzed. According to the study results, 33.1% of included patients received erythropoietin five times or more, corresponding to the study's primary endpoint. It is also worth noting that 66.2% of participants underwent 3 courses of chemotherapy before the start of the drug administration, which emphasizes the relevance of using erythropoietin in treating anemia caused by cytostatic therapy. Twenty-five participants (18.8%) received 2 courses of chemotherapy, and in 3 patients, chemotherapy was administered once (2.3%). The proportion of patients who received chemotherapy 4 to 7 times was 11.4%.

Red blood cell and hemoglobin values were assessed each visit before and after erythropoietin administration. No statistically significant changes were found between visits between RBC count and hemoglobin levels (Table 2).

Table 2 – Dynamics of RBC count and hemoglobin levels before erythropoietin administration

Indicator	Month 1	Month 2	Month 3	r*
Erythrocytes	3.2 (3.0-3.5)	3.1 (2.9-3.5)	3.2 (2.9-3.6)	0.221
Hemoglobin	93.0 (87.0-96.0)	92.0 (85.0-95.0)	92.0 (86.0-96.0)	0.125

*Note: *Friedman criterion*

With the introduction of erythropoietin, positive dynamics of erythrocyte and hemoglobin indices were demonstrated in each observation period. During the 1st and 2nd months of observation, with the introduction of the drug, erythrocyte indices increased by 0.2 10^{12}/L ($p<0.001$) and by 0.3 10^{12}/L ($p<0.001$) in the 3rd month. Positive dynamics of hemoglobin indices gave a difference of 0.6 g/l ($p<0.001$) in the 1st and 3rd months of observation and by 0.4 g/l in the 2nd month ($p<0.001$). Taking into account that the clinical course of malignant neoplasms in most cases is accompanied by the development of anemia both as a result of treatment (chemotherapy) and as a result of impaired erythropoietin response, the above dynamics of indices shows excellent results of using the drug [4]. Table 3 shows the data on the effect of erythropoietin administration on blood parameters (hemoglobin, erythrocytes) during the observation period. Statistically significant differences in blood parameters before and after administration of the drug were found for all months of observation.

Table 3 – Effect of erythropoietin administration on blood parameters (hemoglobin, erythrocytes) according to 1-3 months of observation

Indicators	Month of observation					
	1	p*	2	p*	3	p*
Erythrocytes, before the introduction of EZ	3.2 (3.0-3.5)	<0.001	3.1 (2.9-3.5)	<0.001	3.2 (2.9-3.6)	<0.001
Erythrocytes after administration of EZ	3.4 (3.1-3.9)		3.3 (3.0-3.7)		3.5 (3.2-3.8)	
Hemoglobin, before the introduction of EZ	93.0 (87.0-96.0)	<0.001	92.0 (85.0-95.0)	<0.001	92.0 (86.0-96.0)	<0.001
Hemoglobin after administration of EZ	99.0 (91.5-102.5)		96.0 (92.0-101.0)		98.0 (91.0-104.0)	

*Note: *Wilcoxon test*

No statistically significant differences were found when studying the effect of the number of chemotherapy courses on RBC count and hemoglobin levels (Table 4).

Table 4 – Effect of the number of chemotherapies on blood parameters before the introduction of erythropoietin according to visit data

Indicators	Number of chemotherapy treatments			r*
	1-2	3	4 or more	
Erythrocytes	3.2 (2.8-3.9)	3.2 (3.0-3.4)	3.3 (3.1-3.8)	0.592
Hemoglobin	89.0 (83.0-96.5)	93.0 (88.0-96.5)	94.0 (90.0-97.0)	0.234

*Note: *Kruskal-Wallis test, no statistically significant differences found*

Table 5 shows the data on the effect of the number of erythropoietin administrations on hemoglobin and erythrocyte indices. A positive increase in RBC counts and hemoglobin levels was noted after chemotherapy with the administration of erythropoietin in the 1st month of observation. Despite the administration of chemotherapeutic drugs, the differences in the median values of the difference in both the number of erythrocytes and the hemoglobin level are statistically significant. The increase was more pronounced with two and three intakes of the drug. A higher hemoglobin difference was noted with three or more administrations - 10.0 (6.0; 16.0), and erythrocytes with two administrations - 0.23 (-0.02; 0.48). In the second and third months of observation, increases in erythrocyte and hemoglobin indices were recorded in all groups after administering the drug. The greatest increase was noted with three or more administrations of the drug, but these differences are not statistically significant.

Table 6 shows the direction of changes in RBC count and hemoglobin levels by months of observation.

Table 5 – Effect of the number of erythropoietin administrations on the difference in blood parameter values according to 1-3 months of observations

Indicators	Number of erythropoietin injections			r*
	1	2	3 or more	
After 1 month (n=128)				
Median difference in RBC counts before and after chemotherapy	0.10 (-0.03; 0.25)	0.23 (-0.02; 0.48)	0.20 (0.13; 0.40)	0.043
Median difference in hemoglobin levels before and after chemotherapy	3.0 (1.0; 8.0)	7.0 (2.0; 13.0)	10.0 (6.0; 16.0)	0,001
After 2 months (n=122)				
Median difference in RBC counts before and after chemotherapy	0.18 (0.03; 0.35)	0.19 (0.01; 0.40)	0.43 (0.28; 0.55)	0.198
Median difference in hemoglobin levels before and after chemotherapy	4.0 (2.0; 9.0)	5.0 (1.0; 7.0)	15.0 (9.5; 19.0)	0.062
After 3 months (n=109)				
Median difference in RBC counts before and after chemotherapy	0.21 (0.04; 0.46)	0.28 (0.07; 0.51)	0.16 (0.10; 0.36)	0.976
Median difference in hemoglobin levels before and after chemotherapy	5.0 (2.0; 10.0)	8.5 (4.0; 15.0)	4.0 (3.5; 11.0)	0.296

*Note: *Kruskal-Wallis test*

Table 6 – Direction of changes in blood parameters by month against the background of erythropoietin intake (n=133)

Indicator	Month 1	Month 2	Month 3
Erythrocytes			
Decrease	3 4 (25.6%)	23 (17.3%)	18 (13.5%)
No changes	4 (3.0%)	2 (1.5%)	4 (3.0%)
Increase	90 (67.7 %)	97 (72.9%)	87 (65.4%)
No data	5 (3.8%)	11 (8.3%)	24 (18.0%)
Hemoglobin			
Decrease	21 (15.8%)	13 (9.8%)	14 (10.5%)
No changes	3 (2.3%)	5 (3.8%)	1 (0.8%)
Increase	104 (78.2%)	104 (78.2%)	94 (70.7%)
No data	5 (3.8%)	11 (8.3%)	24 (18.0%)

During the study, no serious or serious events or deaths were recorded in patients, confirming the good tolerability of erythropoietin.

Discussion: The results of our study confirm the high efficiency and safety of erythropoietin in the correction of anemia in cancer patients receiving chemotherapy. Positive dynamics of hemoglobin levels in 78.2% and erythrocytes in 65.4% of patients indicate a significant effect of the drug on improving hematological parameters.

Anemia associated with cancer and its treatment is a serious problem affecting the quality of life of patients and the effectiveness of antitumor therapy [5]. As shown by the results of our study, the hemoglobin level increased by 0.6 g/L ($p<0.001$) during the first month and by 0.4 g/L ($p<0.001$) in the second month, which confirms the relevance of using erythropoietin as a means for correcting anemia.

Using erythropoietin in clinical practice can significantly reduce the need for blood transfusions [6], which is especially important in resource-limited settings and the increasing number of patients with anemia. Reducing the frequency of red blood cell transfusions helps to reduce the risks associated with this procedure, such as complications and transmission of infections through donor blood components. No serious adverse events were reported in our study, which underlines the safety profile of erythropoietin.

Our study data are consistent with the results of other clinical trials that have reported erythropoietin's efficacy in treating anemia in cancer patients [7]. For example, the ORHEO post-marketing study demonstrated that 81.6% of patients responded to erythropoietin therapy within three months, confirming its reliability as a tool for correcting anemia [8].

Conclusion: The main objectives and purpose of the study were achieved. The study included a planned sample according to the protocol. Data on using erythropoietin in real clinical practice for anemia caused by cytostatic therapy in patients with verified solid cancer of any localization were collected and described. The clinical and demographic characteristics of the patients were described. The data obtained indicate a significant predominance of women among patients with anemia, which may be associated with the high incidence of breast cancer and gynecological tumors, as well as the peculiarities of the pathogenesis of anemia in this group. The average age of patients (60 years) and normal body mass index in most participants indicate the need for an individualized approach to correcting anemia, taking into account age and risk factors. A high proportion of patients with gastrointestinal tumors emphasizes the importance of timely detection and treatment of anemia in this category of patients since absorption disorders and blood loss can aggravate the course of the disease.

The drug's efficacy in patients with verified solid cancer has been demonstrated, and positive dynamics of RBC count and hemoglobin levels have been noted in each of the observed periods. Considering that the clinical course of malignant neoplasms in most cases is accompanied by the development of anemia both as a result of treatment (chemotherapy) and as a result of impaired erythropoietin response [4, 9], the above dynamics of indices demonstrate excellent results of drug use.

The high frequency of erythropoietin administration and the absence of reported adverse reactions confirm its favorable safety profile and good tolerability in cancer patients with anemia. These studies demonstrate that five or more times the drug is administered contributes to a stable increase in hemoglobin levels, which allows us to recommend this treatment regimen for effective correction of anemia in real clinical practice.

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АҢДАТПА

ЭРИТРОПОЭТИННІҢ ХИМИОТЕРАПИЯ АЛАТЫН ОНКОЛОГИЯЛЫҚ НАУҚАСТАРДАҒЫ АНЕМИЯНЫ ТҮЗЕТУДЕГІ ТИІМДІЛІГІ

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Өзектілігі: *Анемия – онкологиялық пациенттерде жиі кездесетін асқыну, ол өмір сүру сапасын төмендетіп, ісікке қарсы терапияның тиімділігін нашарлатуы мүмкін. Солидті ісіктері бар пациенттер арасында оның жиілігі 40%-ға, ал химиотерапия кезінде 54%-ға дейін жетеді. Пациенттердің жағдайының нашарлауы химиотерапиямен индуцирленген миелосупрессиямен байланысты, бұл анемияны түзетуді маңызды міндетке айналдырады. Дәрілік түзетудің негізгі әдісі – қан түзілу жүйесінің эритроидты өсуін ынталандыратын эритропоэтиндерді қолдану.*

Мақсаты: *Химиотерапия алатын онкологиялық пациенттерде анемияны түзетуде эритропоэтиннің тиімділігі мен қауіпсіздігін бағалау, нақты клиникалық практикада гематологиялық көрсеткіштерді түзету арқылы емдеу нәтижелерін жақсартуға баса назар аудару.*

Әдістері: *Бұл проспективті интервенциялық емес зерттеуге Қазақстанның екі клиникалық орталығынан 133 пациент қатысты. Қатысу критерийлері: жас ≥18 жыл, верификацияланған солидті ісік, анемия (Hb ≤100 г/л) және жүргізілетін химиотерапия. Зерттеуге 100 (75,2%) әйел және 33 (24,8%) ер адам кірді. Орташа жас – 60 жыл (52,0-67,5). Препарат 78,2% пациентке 3-тен 5 ретке дейін және 21,8% пациентке 1-2 рет енгізілді. Статистикалық талдау Фридман және Вилкоксон критерийлерін пайдалана отырып жүргізілді, маңыздылық деңгейі $p<0,05$.*

Нәтижелері: *133 пациенттің деректері талданды. 65,4-78,2% пациентте гемоглобин мен эритроциттер деңгейінің жоғарылауы байқалды. Бірінші және үшінші айларда гемоглобин деңгейі 0,6 г/л-ге ($p<0,001$), эритроциттер деңгейі 0,2-0,3×10^{12}/л-ге ($p<0,001$) артты. 33,1% пациент препаратты бес және одан да көп рет қабылдады. Елеулі жағымсыз құбылыстар тіркелген жоқ.*

Қорытынды: *Эритропоэтин клиникалық көрсеткіштердің статистикалық тұрғыдан елеулі жақсарғанын көрсетті, бұл оның химиотерапия алатын онкологиялық пациенттерде анемияны түзетудегі тиімділігі мен қауіпсіздігін растайды. Бұл өмір сүру сапасын арттыруға және емдеу нәтижелерін жақсартуға ықпал етеді.*

Түйінді сөздер: *анемия, онкологиялық аурулар, химиотерапия, эритропоэтин, эритропоэз, анемияны түзету, биосимиляр, солидті ісіктер.*

АННОТАЦИЯ

ЭФФЕКТИВНОСТЬ ЭРИТРОПОЭТИНА В КОРРЕКЦИИ АНЕМИИ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ, ПОЛУЧАЮЩИХ ХИМИОТЕРАПИЮ

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Актуальность: *Анемия – частое осложнение у онкологических пациентов, которое снижает качество жизни и может ухудшать эффективность противоопухолевой терапии. Ее частота среди пациентов с солидными новообразованиями достигает 40%, а во время химиотерапии – 54%. Ухудшение состояния пациентов связано с миелосупрессией, вызванной химиотерапией, что делает коррекцию анемии важной задачей. Основным методом медикаментозной коррекции является применение эритропоэтинов, стимулирующих пролиферацию эритроидного ростка кроветворения.*

Цель исследования *– оценка эффективности и безопасности эритропоэтина в коррекции анемии у онкологических пациентов, получающих химиотерапию, с акцентом на улучшение результатов лечения путем коррекции гематологических показателей в реальной клинической практике.*

Методы: *В данном проспективном неинтервенционном исследовании участвовали 133 пациента из двух клинических центров Казахстана. Критерии включения: возраст ≥18 лет, верифицированный солидный рак, анемия (Hb≤100 г/л) и проводимая химиотерапия. Выборку составили 100 – (75,2%) женщин и 33 (24,8%) мужчины. Средний возраст – 60 лет (52,0-67,5). Препарат вводили от 3 до 5 раз у 78,2% пациентов и от 1 до 2 раз – у 21,8% пациентов. Статистический анализ проведен с использованием критериев Фридмана и Вилкоксона, уровень значимости $p<0,05$.*

Результаты: *Проанализированы данные 133 пациентов. У 65,4-78,2% пациентов наблюдалось увеличение уровня гемоглобина и эритроцитов. В первом и третьем месяцах уровень гемоглобина повысился на 0,6 г/л ($p<0,001$), уровень*

эритроцитов – на 0,2-0,3×10¹²/л (p<0,001). 33,1% пациентов получали препарат пятикратно и более. Серьезных нежелательных явлений не зарегистрировано.

Заключение: *Эритропоэтин продемонстрировал статистически значимое улучшение клинических показателей, подтверждая его эффективность и безопасность в коррекции анемии у онкологических пациентов, что способствует повышению качества жизни и улучшению результатов лечения.*

Ключевые слова: *анемия, онкологические заболевания, химиотерапия, эритропоэтин, эритропоэз, коррекция анемии, биосимиляр, солидные опухоли.*

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BRCA-ASSOCIATED OVARIAN CANCER: EXPERIENCE PERSONALIZED TREATMENT. A CLINICAL CASE

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ABSTRACT

Relevance: *Ovarian cancer is one of the deadliest gynecological tumors, claiming the lives of thousands of women every year. Late diagnosis (more than 70% of cases at stage III-IV) is due to the absence of specific symptoms and low screening effectiveness. A personalized treatment approach, including the analysis of BRCA1/2 mutations and the use of PARP inhibitors, has become a significant achievement. Detection of BRCA1/2 mutations has important prognostic value, contributing to early risk prediction and mortality reduction. Genetic counseling for patients with hereditary predispositions allows for prevention through early diagnosis, targeted therapy, and preventive interventions.*

The study aimed to *analyze a clinical case of treatment of a patient with BRCA-associated ovarian cancer with a rare form of mutation for the possibility of personalizing the treatment.*

Methods: *This study presents a clinical case of a patient with advanced ovarian cancer associated with a rare BRCA1 mutation. Mutation detection was performed using sequencing, while treatment efficacy was assessed through computed tomography and measurement of CA-125 levels.*

Results: *The tumor process was stabilized for more than three years. Comprehensive treatment (diagnostic laparoscopy, chemotherapy, surgery, targeted and supportive therapy) stabilized the tumor process. Genetic testing has made it possible to adapt therapy, improving the prognosis. The next of kin were tested for prevention.*

Conclusion: *A personalized approach with BRCA1/2 mutation analysis and PARP inhibitors improves clinical outcomes. Advances in molecular oncology have increased patient survival. However, problems remain: resistance to therapy, limited efficacy in patients without BRCA mutations, and the need for further research into the mechanisms of interaction of PARP inhibitors with other drugs.*

Keywords: *ovarian cancer, BRCA1 and BRCA2 mutations, chemotherapy, PARP inhibitors, a clinical case.*

Introduction: Ovarian cancer is one of the most lethal forms of gynecological tumors, annually taking the lives of tens of thousands of women worldwide [1]. A characteristic disease feature is late diagnosis, which occurs at stage III-IV in more than 70% of cases [2]. This is due to the absence of specific symptoms in the early stages and the insufficient effectiveness of screening methods. A personalized approach to treatment based on the analysis of *BRCA1/2* mutations and the use of PARP inhibitors has become a significant step forward in the fight against this disease.

According to GLOBOCAN 2020, approximately 313,000 new cases of ovarian cancer and 207,000 deaths are reported worldwide annually [1]. In Kazakhstan, more than 1,200 new cases of ovarian cancer are registered annually, accounting for 2.9% of the overall structure of oncological diseases as of 2020. Over the past 15 years, there has been a 21% increase in the detection of ovarian cancer [2]. Projections suggest that by 2040, the incidence will increase by 5%, driven by population aging and growth [3]. *BRCA1* and *BRCA2* are tumor suppressor genes involved in DNA repair through homologous recombination. Their dysfunction leads to the accumulation of DNA damage and increased genomic instability [4]. *BRCA* mutations are associated with heightened sensitivity to platinum-based chemotherapy and PARP inhibitors [5]. Studies have demonstrated that patients with *BRCA* mutations have better progression-free survival (PFS) outcomes than patients without mutations. In the SOLO-1 study, 50% of patients receiving olaparib showed no disease progression over five years [6]. Platinum-based chemotherapy remains the cornerstone of ovarian cancer treatment. Drugs such as carboplatin and paclitaxel are effective in the initial treatment stages, but the high recurrence rate underscores the need for maintenance therapy [7]. PARP inhibitors (olaparib) have become central to maintenance therapy. These drugs block the DNA repair system, inducing apoptosis in tumor cells with *BRCA* mutations [8]. SOLO-1 Study: Olaparib extended median PFS to 56 months in patients with *BRCA* mutations [6]. PRIMA Study: Niraparib demonstrated efficacy in *BRCA*-mutated and non-mutated patients, increasing PFS by 13.8 months [9]. ARIEL-3 Study: Rucaparib significantly improved PFS in patients with recurrent disease [10]. The PAOLA-1 studies evaluated the combination of PARP inhibitors with bevacizumab, an antiangi-

ogenic drug. In patients with *BRCA* mutations, the combination of olaparib and bevacizumab extended PFS to 37.2 months compared to 17.7 months in the control group [11]. Modern technologies such as next-generation sequencing (NGS) support identifying *BRCA* mutations and determining the levels of genomic instability, which are critical factors in choosing therapy [12]. Prognostic markers include homologous recombination deficiency (HRD) status and PARP1 expression levels [13].

Objective: to analyze and describe a clinical case of treatment of a patient with *BRCA*-associated ovarian cancer with a rare form of mutation with the possibility of personalizing therapy.

Material and Methods: This study presents a clinical case of a patient with advanced ovarian cancer associated with a rare *BRCA1* mutation, receiving treatment at the Almaty Oncology Center in Kazakhstan. To identify mutations in the *BRCA1* and *BRCA2* genes, mass parallel sequencing (NGS) was performed on the MiniSeq platform (Illumina) using the AmpliSeq® *BRCA* Panel for Illumina reagent kit (Illumina, San Diego, CA, USA), which is a targeted panel covering all exon regions and flanking intron sequences of the *BRCA1* and *BRCA2* genes. Given the patient's age and sensitivity to platinum-based therapy, a rare *BRCA1* mutation was detected. The effectiveness of treatment was monitored using computed tomography (CT) and CA-125 tumor marker levels.

Clinical case:

Patient Information: Patient A, born in 1978 (age at diagnosis – 43 years), visited the Almaty Oncology Center (Almaty, Kazakhstan) complaining of increased weakness and abdominal volume. It is known from the anamnesis that the patient's mother had endometrial cancer, and two relatives had breast cancer. The patient noted a deterioration in her health since July 2021, when the above symptoms appeared, after which she sought medical help.

Clinical data: The functional status was assessed at 2 points on the ECOG scale during the initial examination. A significant amount of free fluid in the abdominal cavity was revealed among the critical symptoms.

Diagnostics: Clinical tests at the visit revealed anemia (hemoglobin 92 g/L, erythrocytes 3.2×10^9/L). No other clinically significant deviations were noted. The CA-125 tumor marker level as of 08/10/2021 was 289 U/mL. CT scanning of the chest on 08/12/2021 found no infiltrative changes. CT scan of the abdomen and pelvis on 07/20/2021 revealed a soft tissue formation in the pelvis originating from the left ovary and massive ascites.

Diagnostic laparoscopy revealed peritoneal carcinomatosis affecting up to 70% of the peritoneum, a tumor conglomerate in the pelvis with no clear organ differentiation, and ascites up to 6000 mL, which was evacuated. Morphological examination confirmed the diagnosis as metastatic adenocarcinoma (tumor biopsy). The final diagnosis was stage IIIc ovarian cancer (T3cNxM0) with carcinomatosis of the abdomen and pelvis and ascites.

Treatment: Given the extent of the disease, the patient's condition, and the lack of technical feasibility for optimal surgical intervention, it was decided to initiate platinum-based chemotherapy. From October 14, 2021, to February 22, 2022, the patient received six courses of neoadjuvant chemotherapy with the following regimen: carboplatin AUC5 and paclitaxel 175 mg/m^2. During antitumor therapy, the patient's condition improved significantly. Functional status improved to 1 point on the ECOG scale, moderate weakness persisted, and anemia resolved, with hemoglobin levels increasing to 124 g/L.

The patient underwent chemotherapy with asthenia and thrombocytosis. Control Computed tomography of the chest, abdomen and pelvis with intravenous contrast (03/09/2022) showed a decrease in the size of the retroperitoneal lymph nodes and no changes in the nodular formations along the anterior abdominal wall, an increase in the size of the uterine body and inguinal lymph nodes was recorded. Colonoscopy with biopsy showed a morphological picture characteristic of carcinoma. 01/20/2022, and positive dynamics in stabilizing the level of the CA-125 tumor marker to 18 U/mL were recorded.

On March 30, 2022, interval cytoreduction was performed, including laparotomy, total hysterectomy with bilateral salpingo-oophorectomy, resection of the sigmoid colon with a side-to-side anastomosis, and omentectomy. The postoperative period was uneventful.

According to the results of morphological examination of the postoperative material, serous cystadenocarcinoma of the ovary (G3) was revealed with signs of decay, minimal signs of therapeutic pathomorphosis, germination of all layers of the colon wall and adjacent adipose tissue. No tumor cells were found at the resection edges; there are also no signs of a tumor in the omentum tissue and lymph node.

On 19.04.2022, the CA-125 tumor marker level was 13.75 U/mL. From 13.04.2022 to 30.06.2022, the patient underwent four courses of adjuvant chemotherapy with targeted therapy in the following regimen: carboplatin (AUC5), paclitaxel 175 mg/m^2, and bevacizumab 700 mg (10 mg/kg). The therapy was well tolerated against the concomitant treatment.

On 29.07.2022, the CA-125 tumor marker level was 23.00 U/mL.

Control CT of the chest, abdomen and pelvis with intravenous contrast from 22.07.2022 revealed metastatic lesions of the iliac lymph nodes and lymphadenopathy of the inguinal lymph nodes (Figure 1).

From 10.08.2022 to 26.10.2022, four courses of chemotherapy with targeted therapy were administered in the following regimen: gemcitabine 1600 mg intravenously by drip on the 1st and 8th days of the cycle and bevacizumab 700 mg (10 mg/kg) intravenously by drip. The patient tolerated the treatment satisfactorily despite concomitant therapy.

On 10.10.2022, the CA-125 tumor marker level was 4.52 U/mL.

Control CT of the chest, abdomen and pelvis with intravenous contrast on 07.11.2022 confirmed the presence of metastatic lesions of the iliac lymph nodes and lymphadenopathy of the inguinal lymph nodes. The comparison with the CT of 22.07.2022 revealed no significant dynamics (Figure 2).

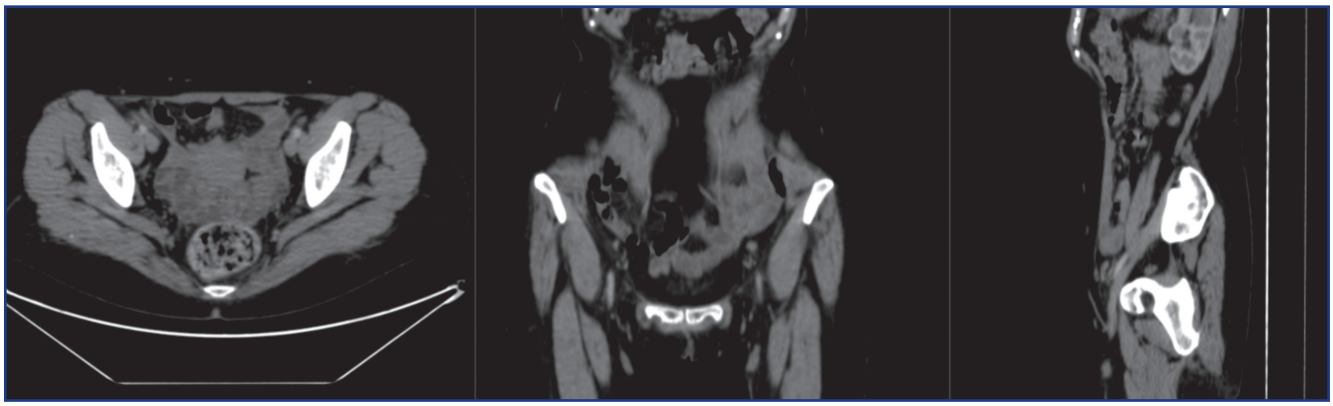

Figure 1 – CT of the chest, abdomen and pelvis with intravenous contrast on July 22, 2022

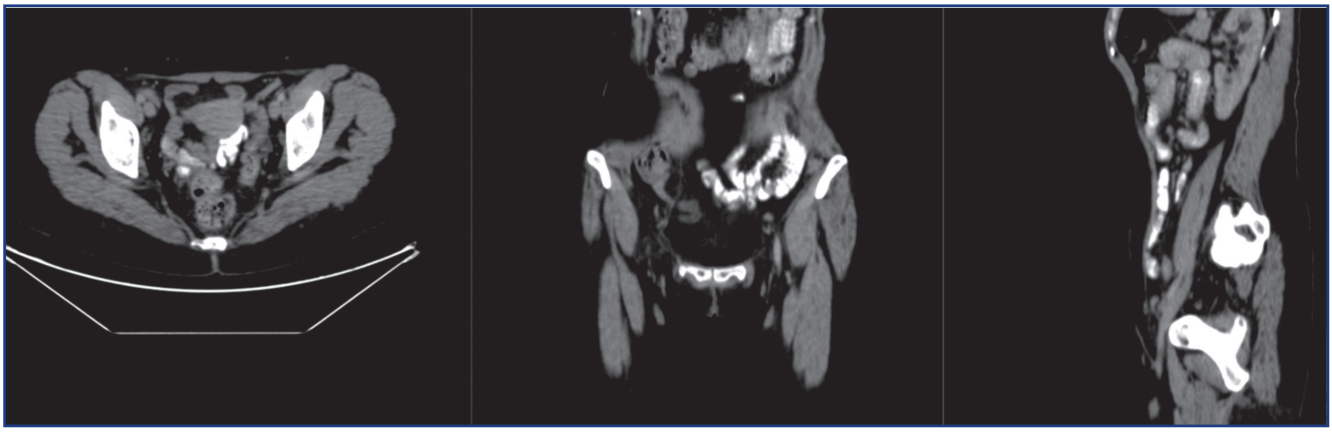

Figure 2 – CT of the chest, abdomen and pelvis with intravenous contrast on November 07, 2022

According to the council's decision, from November 25, 2022, to February 8, 2023, four more courses of chemotherapy with targeted therapy were administered in the following regimen: gemcitabine 1600 mg intravenously by drip on the 1st and 8th days of the cycle and Bevacizumab 800 mg (10 mg/kg) intravenously by drip. On February 21, 2023, the patient received targeted monotherapy with bevacizumab at a dose of 800 mg, which was administered intravenously by drip infusion. On 17.02.2023, the CA-125 tumor marker level was 7.25 U/mL. Control CT of the chest, abdomen and pelvis with intravenous contrast from 03.01.2023 showed an increase in the size of the iliac lymph nodes compared to the CT data from 11.07.2022, which indicates the progression of the process (Figure 3).

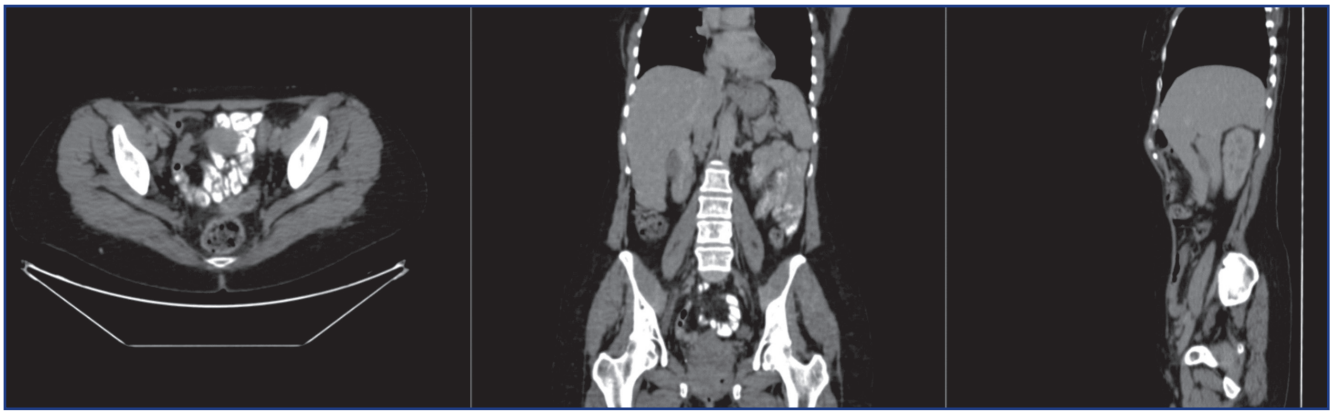

Figure 3 – CT of the chest, abdomen and pelvis with intravenous contrast on January 03, 2023

According to clinical recommendations, the patient underwent four courses of anti-relapse chemotherapy (PCT) from June 16 to August 21, 2023, in carboplatin AUC5 and paclitaxel 175 mg/m^2 regimen. Monitoring of the tumor marker CA-125 level showed a value of 24.8 U/mL on 18.08.2023, and 31.6 U/mL on 14.09.2023. Postoperative material was sent for testing for mutations in the *BRCA* gene. In a heterozygous state, a pathogenic variant was detected in the *BRCA1* gene NM_007294.4 (*BRCA1*); c181T>G (p.Cys61GLY). Given this genetic change and platinum-sensitive relapse of serous epithelial ovarian cancer, since November 2023, the patient has been receiving

maintenance therapy with the PARP inhibitor olaparib at a dosage of 600 mg per day (2 capsules 2 times a day). The drug was provided as part of charitable assistance by "Kazakhstan Khalkyn" Public Fund. During olaparib therapy, the patient experienced side effects such as nausea and episodes of diarrhea that occurred during the first month of treatment. These adverse events did not require dose adjustment or drug discontinuation.

A control CT scan with intravenous contrast performed on 06.12.2023 showed a picture of metastatic lesions of the iliac lymph nodes and lymphadenopathy of the inguinal lymph nodes. Compared with the CT results of 06.09.2023, an increase in the size of the iliac lymph nodes was observed. The CA-125 tumor marker level was 30.28 U/mL on 28.12.2023, 34.95 U/mL on 17.01.2024, and 37.15 U/mL on 12.02.2024. CT with intravenous contrast of 04.03.2024 showed a further increase in the size of the iliac lymph nodes, with stable sizes of the inguinal lymph nodes. Hyperplasia of the retroperitoneal lymph nodes (suspected metastasis) and an increase in the size of the para-aortic lymph nodes (suspected metastasis) were also detected compared to the CT of 06.12.2023 (Figure 4).

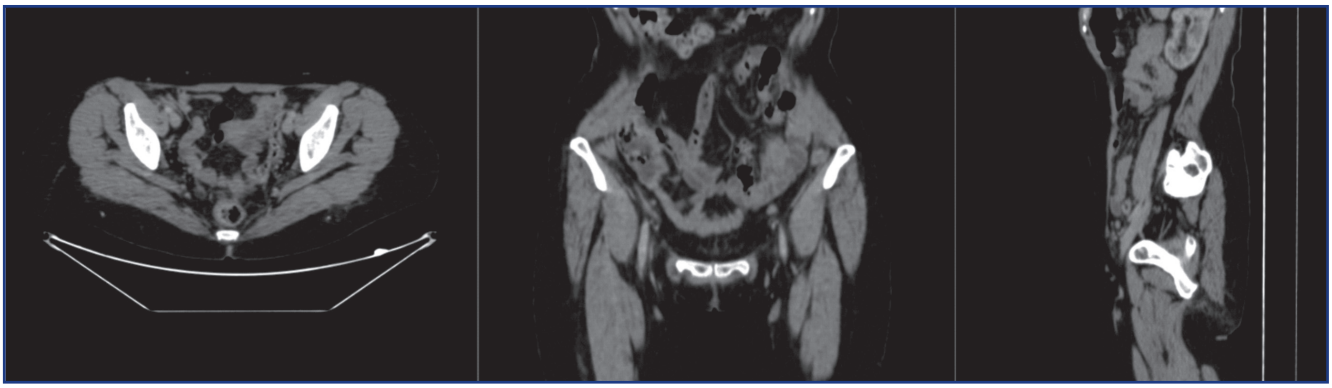

Figure 4 – CT of the chest, abdomen and pelvis with intravenous contrast on March 04, 2024

The CA-125 tumor marker level amounted to 41.0 U/mL on 11.03.2024 and 40.3 U/mL on 10.04.2024. Taking into account the progression of the disease, the patient received eight courses of targeted therapy from 13.05.2024 to 30.10.2024: bevacizumab 900 mg (10 mg/kg) and olaparib 600 mg (2 capsules 2 times a day) on an outpatient basis. The drugs were provided as part of charitable assistance by "Kazakhstan Khalkyna" Public Fund. The patient tolerated the therapy satisfactorily, with accompanying supportive treatment. The patient continues outpatient therapy, receiving Lynparza (olaparib) 600 mg, 2 drops, 2 times a day.

Control CT with intravenous contrast from September 23, 2024, showed mts-lesion of the iliac and para-aortic lymph nodes and lymphadenopathy of the inguinal lymph nodes; a stabilization of the process was noted in comparison with the CT of 04.06.2024 (Figure 5).

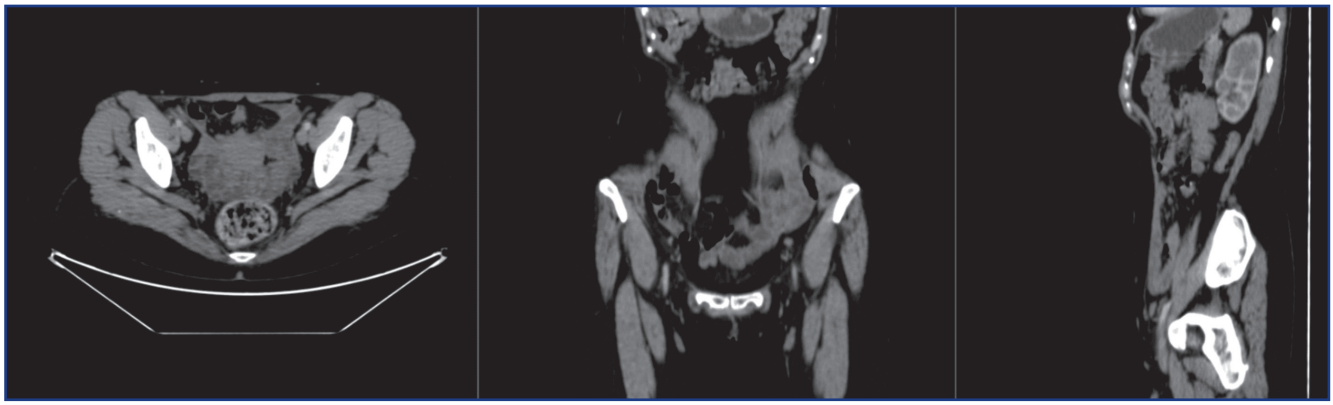

Figure 5 – CT of the chest, abdomen and pelvis with intravenous contrast on September 23, 2024

Results: The comprehensive treatment strategy, including diagnostic laparoscopy, neoadjuvant and adjuvant chemotherapy, surgery, and supportive therapy with PARP inhibitors, has allowed for the stabilization of the tumor process for more than three years.This strategy contributed to tumor stabilization and improved overall clinical outcomes. Genetic testing played a key role in treatment planning, enabling therapy to be tailored to the patient's molecular profile. The identification of a rare *BRCA1* mutation (NM_007294.4 (*BRCA1*); c.181T>G (p.Cys61Gly)) in a heterozygous state confirmed sensitivity to platinum-based chemotherapy and PARP inhibitors, which significantly prolonged disease control. CA-125 tumor marker levels were monitored throughout treatment and correlated with disease progression and therapeutic response. Initially, tumor regression and bio-

chemical remission were achieved; however, subsequent imaging detected metastatic involvement of the iliac and para-aortic lymph nodes, requiring therapy adjustments. The patient continues maintenance treatment with olaparib in combination with bevacizumab, demonstrating disease stabilization with no evidence of new metastatic lesions. Despite periods of disease progression, the personalized treatment strategy has extended progression-free survival and improved the patient's quality of life. This case underscores the importance of individualized therapy in *BRCA*-associated ovarian cancer and highlights the need for further research into resistance mechanisms and the optimization of combination treatment approaches (Table 1).

Table 1 – Timeline of the presented clinical case of ovarian cancer with *BRCA1* mutation

Year	Key Event
2021	Symptom onset (July 2021)
	CA-125: 289 U/mL (August 2021)
	Chest CT: no changes (August 2021)
	Abdominal and pelvic CT: tumor in the left ovary, massive ascites (July 2021)
	Diagnostic laparoscopy, biopsy: peritoneal carcinomatosis (70% of peritoneum), tumor conglomerate, ascites (6000 mL) (August 2021)
2021-2022	Neoadjuvant chemotherapy (Carboplatin AUC5 + Paclitaxel 175 mg/m²) (October 2021 – February 2022)
2022	CT: lymph node reduction (March 2022)
	Interval cytoreduction: laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, sigmoid colon resection, omentectomy (March 2022)
	CA-125: 13.75 U/mL (April 2022)
	Adjuvant chemotherapy + Bevacizumab (April-June 2022)
	Lymph node metastases (CT, July 2022)
	Chemotherapy + Bevacizumab (Gemcitabine) (August-October 2022)
	CA-125: 4.52 U/mL (October 2022)
	Continuation of chemotherapy + Bevacizumab (November 2022 - February 2023)
2023	Bevacizumab monotherapy (February 2023)
	BRCA1 mutation detected (Sequencing, September 2023)
	Anti-relapse chemotherapy (Carboplatin + Paclitaxel) (June-August 2023)
	Olaparib maintenance therapy (November 2023)
	CT: progressive lymphadenopathy (December 2023)
2024	CT: disease progression (March 2024)
	Targeted therapy (Bevacizumab + olaparib) (May-October 2024)
	CT: disease stabilization (September 2024)
	The patient continues maintenance therapy with olaparib and bevacizumab

Discussion: Long-term disease control in a patient with advanced ovarian cancer over three years highlights the effectiveness of a personalized approach based on detecting a germline *BRCA1* mutation. The comprehensive treatment strategy, including diagnostic laparoscopy, neoadjuvant and adjuvant chemotherapy, surgery, and maintenance therapy with a PARP inhibitor, contributed to tumor stabilization.

Identifying a germline *BRCA1* mutation allowed for a tailored therapeutic approach, optimizing treatment outcomes. This case underscores the significance of molecular genetic testing in selecting individualized treatment regimens, thereby enhancing the patient's prognosis. The patient's immediate relatives also underwent *BRCA1* mutation testing for preventive purposes. They were advised to undergo regular medical examinations for early cancer detection and risk reduction if the mutation was detected.

These findings emphasize the value of a personalized approach and highlight the need for further research into genetic factors as essential tools for developing preventive and therapeutic strategies in oncology.

Conclusions: Integrating *BRCA1/2* mutation analysis and PARP inhibitor therapy significantly improves clinical outcomes in ovarian cancer management. Advances in molecular biology and clinical oncology have increased survival rates in *BRCA*-associated ovarian cancer. Furthermore, the introduction of combination therapies, such as PARP inhibitors with antiangiogenic agents, has expanded treatment options.

However, challenges remain, including therapy resistance, limited efficacy in non-*BRCA*-mutated patients, and the need for further investigation into PARP inhibitor interactions with other therapeutic agents. Addressing these issues requires additional studies to optimize clinical practice and improve patient outcomes.

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АҢДАТПА

BRCA-БАЙЛАНЫСТЫ АНАЛЫҚ БЕЗ ҚАТЕРЛІ ІСІГІ: ЖЕКЕ ЕМДЕУ ТӘЖІРИБЕСІ. КЛИНИКАЛЫҚ ЖАҒДАЙ

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Өзектілігі: *Аналық без қатерлі ісігі-жыл сайын мыңдаған әйелдердің өмірін қиатын ең қауіпті гинекологиялық ісіктердің бірі. Кеш диагноз (III-IV сатыдағы жағдайлардың 70% - дан астамы) нақты белгілердің болмауына және скринингтің төмен тиімділігіне байланысты. Емдеуге жекелендірілген тәсіл, соның ішінде BRCA1/2 мутациясын талдау және PARP ингибиторларын қолдану маңызды жетістік болды. BRCA1/2 мутацияларын анықтау тәуекелді ерте болжауға және өлімді азайтуға ықпал ететін маңызды болжамдық мәнге ие. Тұқым қуалайтын бейімділігі бар науқастарға генетикалық кеңес беру ерте диагностика, мақсатты терапия және алдын алу шаралары арқылы алдын алуға мүмкіндік береді.*

Мақсаты *– терапияны жекелендіру мүмкіндігі және мутацияның сирек түрі бар BRCA-мен байланысты аналық без қатерлі ісігі бар науқасты емдеудің клиникалық жағдайын талдау және сипаттау.*

Әдістері: *Бұл зерттеуде сирек кездесетін BRCA1 мутациясымен байланысты аналық бездің қатерлі ісігі бар науқастың клиникалық жағдайы келтірілген. Мутацияларды анықтау реттілік арқылы жүргізілді және емдеудің тиімділігі КТ және СА-125 деңгейін өлшеу арқылы бағаланды.*

Нәтижелері: *Ісік процесі үш жылдан астам тұрақтандырылды. Кешенді емдеу (диагностикалық лапароскопия, химиотерапия, хирургия, мақсатты және қолдау терапиясы) ісік процесін тұрақтандырды. Генетикалық тестілеу болжамды жақсарту арқылы терапияны бейімдеуге мүмкіндік берді. Алдын алу үшін жақын туыстарына тестілеу жүргізілді.*

Қорытынды: *BRCA1/2 мутациясын және PARP ингибиторларын талдаумен жекелендірілген тәсіл клиникалық нәтижелерді жақсартады. Молекулалық онкологиядағы жетістіктер пациенттердің өмір сүруін арттырды. Алайда, кемшіліктер бар: терапияға төзімділік, BRCA мутациясы жоқ науқастарда тиімділігі шектеулі, PARP ингибиторларының басқа препараттармен өзара әрекеттесу механизмдерін одан әрі зерттеу қажеттілігі.*

Түйін сөздер: *аналық без қатерлі ісігі, BRCA1 жен BRCA2 мутациясы, химиотерапия, PARP ингибиторлары, клиникалық жағдай.*

АННОТАЦИЯ

BRCA-АССОЦИИРОВАННЫЙ РАК ЯИЧНИКОВ: ОПЫТ ПЕРСОНАЛИЗИРОВАННОГО ЛЕЧЕНИЯ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Рак яичников – одна из самых смертоносных гинекологических опухолей, ежегодно уносящая жизни тысяч женщин. Поздняя диагностика (более 70% случаев на III-IV стадии) обусловлена отсутствием специфических симптомов*

и низкой эффективностью скрининга. Значительным достижением стал индивидуальный подход к лечению, включающий анализ мутаций BRCA1/2 и использование ингибиторов PARP.

Выявление мутаций BRCA1/2 имеет важное прогностическое значение, способствуя раннему прогнозированию риска и снижению смертности. Генетическое консультирование пациентов с наследственной предрасположенностью позволяет проводить профилактику с помощью ранней диагностики, таргетной терапии и профилактических вмешательств.

***Цель исследования** – проанализировать и описать клинический случай лечения пациентки с BRCA-ассоциированным раком яичников с редкой формой мутации с возможностью персонализации терапии.*

***Методы:** В данном исследовании представлен клинический случай пациентки с распространенным раком яичников, ассоциированным с редкой мутацией BRCA1. Выявление мутаций проводилось с помощью секвенирования, а эффективность лечения оценивалась с помощью компьютерной томографии и измерения уровня CA-125.*

***Результаты:** Опухолевый процесс был стабилизирован более чем на три года. Комплексное лечение (диагностическая лапароскопия, химиотерапия, хирургическое вмешательство, таргетная и поддерживающая терапия) стабилизировало опухолевый процесс. Генетическое тестирование позволило адаптировать терапию, улучшив прогноз. Ближайшие родственники прошли профилактическое обследование.*

***Заключение:** Индивидуальный подход с использованием анализа мутаций BRCA1/2 и ингибиторов PARP улучшает клинические результаты. Достижения в области молекулярной онкологии позволили увеличить выживаемость пациентов. Однако проблемы остаются: резистентность к терапии, ограниченная эффективность у пациентов без мутаций BRCA и необходимость дальнейших исследований механизмов взаимодействия ингибиторов PARP с другими лекарственными средствами.*

***Ключевые слова:** рак яичников, мутации BRCA1 и BRCA2, химиотерапия, ингибиторы PARP, клинический случай.*

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PALLIATIVE CARE FROM A MOBILE TEAM FOR A PATIENT WITH METASTATIC BREAST CANCER AT HOME: A CLINICAL CASE

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ABSTRACT

Relevance: *Palliative care aims to improve patient care by correctly diagnosing and effectively treating pain and other severe symptoms that worsen the patient's condition. It also includes educating relatives about care and providing psychological and social support to the patient and his/her family.*

The purpose was to *study the role of a mobile team in providing comprehensive palliative care at home to a patient diagnosed with tumor-infiltrative breast cancer with metastatic lesions.*

Methods: *The article presents a clinical case of a patient with tumor-infiltrative breast cancer of stage III B, complicated by metastases to the brain and pelvic bones and bedsores of stage III-IV. The disease progressed despite four cycles of neoadjuvant polychemotherapy and four cycles of targeted therapy. Special attention is paid to the work of the visiting team, which provides comprehensive medical, psychological, and social support to the patient and his/her family at home. The main aspects of palliative care include competent identification and effective management of pain symptoms, care and treatment of bedsores, nasogastric tube feeding, and interaction with family members to reduce emotional stress.*

Results: *Treatment of stage III-IV bedsores gave positive dynamics in the form of transition to the granulation phase after 1.5 months of conservative therapy. Modern wound treatment methods, including antiseptic solutions and antibiotic ointments, helped reduce infectious complications and improve the patient's condition. The work of the mobile team highlighted the importance of an individualized approach that includes both medical and social support within palliative care.*

Conclusions: *Mobile teams providing palliative care at home to severe terminal cancer patients improve their quality of life and satisfaction with the care provided.*

Keywords: *breast cancer, tumor-infiltrative form, palliative care, mobile team, bedsores treatment, metastases, quality of life.*

Introduction: Treatment of patients with metastatic forms of breast cancer at a late stage is a complex task in modern oncology and requires a comprehensive approach, including palliative care. This approach is based on early diagnosis and personalized treatment to improve the quality of life and reduce the symptom burden [1, 2].

The tumor-infiltrative form of breast cancer accompanied by metastatic bone and brain involvement is characterized by rapid progression and severe course, as in the presented case. In cases of significant deterioration of the patient's condition, neoadjuvant polychemotherapy (NAPCT), targeted therapy (TT), and palliative radiotherapy are becoming the standard of care for such forms despite limited resources and high complication rates [3, 4].

Stage III B breast cancer is complicated by brain and pelvic metastases and degree III-IV skin ulcers. This emphasizes the importance of a timely multidisciplinary approach, including the involvement of a mobile palliative care team that provides medical care and psychosocial support to the family [5, 6].

The study aimed to investigate the role of a mobile team providing comprehensive palliative care at home to a patient diagnosed with tumor-infiltrative breast cancer with metastatic lesions.

Materials and methods: This article presents a clinical case of a patient diagnosed with stage III B infiltrative breast cancer complicated by metastases to the brain and pelvis and the development of degree III-IV skin ulcers.

Clinical case:

Patient information: Patient K., 76 years old. Clinical diagnosis: Cancer of the left breast, stage IIIB (T4N1M0). Type I - infiltrative. Status after 4 cycles of NAFT treatment. Accelerated process with brain and pelvic bone involvement with multiple metastases. Status after 4 cycles of NACHT treatment. Right-sided hemiparesis. Skin ulcer of the occipital region, stage III-IV, dry necrosis phase. Additional diagnosis: Arterial hypertension stage 3, risk 4. Coronary heart disease, FC 3. Severe tension angina pectoris. Stage I of chronic heart failure (CHF).

Medical History: The patient has been ill since Spring 2023. Applied to the local polyclinic with complaints of

a thickening in the left breast. 08.06.2023 A targeted ultrasound examination of the left breast at the border of quadrants revealed an irregularly shaped, inhomogeneous structure with a hypoechogenic area of 16×10 mm in size. Conclusion: Dense mass in the left breast (B3-4).

Diagnostics

Histological examination result: No. 21941-42 Infiltrative breast cancer.

IHC study result: No. 1257/23 Morphological picture and immunophenotype are consistent with infiltrative breast cancer, G. II (2+2+3). Her2/neu-positive type. ICD-O code 8500/3.

From 25.08.2023 to 10.11.2023, the patient received 4 inpatient NAFT courses. Manifestations of asthenia and vomiting syndrome accompanied the treatment.

20.12.2023: CT of chest/abdominal/pelvic cavity organs with intravenous contrast agent: CT signs of mass (Cr) in the left breast. Unilateral and bilateral compressed nodules in both lungs and bilateral hydrothorax. Negative dynamics compared to the CT data of 17.07.2023 was manifested by an increase in the mass of the formation.

CT signs: hypodensitis of the liver (mts suspected). Liver cysts, gallbladder obstruction. Cysts of both kidneys and the spleen. Fatty degeneration of the pancreas. Hypodense formations appeared in the liver compared to the CT data of 17.07.2023. CT scan of pelvic organs revealed involutional changes in pelvic organs.

20.12.2023: The result of the echocardiographic study: Echocardiography on the background of arrhythmia. Aortic walls are thickened. The contractility was moderately reduced. No hypokinesia. Small calcificates in the interventricular atrium. Moderate hypertrophy of the left ventricle. Regurgitation in the aortic valve. 20.12.2023 Cardiologist consultation: Diagnosis: Coronary heart disease. Functional class II with increased angina. SNFC II. Arterial hypertension stage 2, risk group 3.

From 04.01.2024 to 17.05.2024: received 4 courses of NACHT treatment. Treatment regimen: Docetaxel 100 mg intravenously, Trastuzumab 324 mg intravenously, Pertuzumab 420 mg intravenously on day 1 of adjuvant therapy.

26.06.2024: CT brain findings: Signs of brain metastases were found in frontal, temporal, occipital, parietal, and cerebellar regions. Left maxillary sinus cysts, subatrophic changes of brain tissue, dyscirculatory encephalopathy.

26.06.2024: CT scan of the chest organs: signs of volumetric mass in the left breast (c-r). Skeletal bone lesions with metastases. Half of the lung nodes are compacted, lymphadenopathy of mediastinal lymph nodes. Acceleration of the process with the appearance of MTS foci.

26.06.2024: CT scan of abdominal cavity organs: signs of liver cysts, gallbladder obstruction. Cysts in the kidneys and spleen. Fatty degeneration of the pancreas. Metastases in the bones of the skeleton.

26.06.2024: CT scan of the pelvic organs: Bladder wall thickening. Metastases to pelvic bones.

From 15.07.2024 to 17.07.2024: Total conformal radiotherapy (3DCRT) with a total focal dose of 9 Gy to the brain areas affected by metastases under the control of an imaging system (IGRT), with comparison of soft tissue and bone structures was performed for palliative purpose. The planned total focal dose was 30 Gy. Due to the deterioration of the patient's condition, the possibility of continuing radiotherapy was discontinued.

29.07.2024: By the decision of the Multidisciplinary Team (MT) No. 9142, due to the acceleration of the process, deterioration of the general condition, pain syndrome, and exacerbation of the tumor toxicity syndrome the patient was assigned to the IV clinical group, and remained under the observation of the visiting team to receive palliative care at home.

31.07.2024: Deadline for applications for assistance to the mobile palliative care team.

Clinical data: 08.01.2024: A physician, nurse, and psychologist initially assessed the patient's condition. The medical examination was conducted in the presence of epy patient's daughter. According to her daughter, the patient complained of anxiety, which was particularly aggravated when the patient changed her body position. The patient's taciturnity did not allow them to localize the painful symptoms. The patient had a nocturnal sleep disturbance not caused by pain. The patient's daughter attributed her mother's deterioration to radiation therapy and reported that her condition had worsened over the past week.

On examination, the patient's condition was extremely severe. The pain score on the PAINAD scale – 3 points.

Neurological status: Level of consciousness – deep shock, unconscious. Meningeal symptoms were negative. Pupil OD=OS, photoreaction was lively. Nystagmus: none. Facial symmetry: Preserved. Right-sided hemiparesis. Numerical cognition could not be assessed. Breathing was even, spontaneous. Auscultation revealed equally diminished breath sounds on both sides. No wheezing was heard. Heart sounds were muffled, and tachycardia was present. Blood pressure: 90/60 mm Hg. Heart rate: 98 beats per minute. Oxygen saturation: 90%. Body temperature: 36.1°C. The patient was motionless and required full assistance. The skin was pale and dry. No shortness of breath or coughing. The tongue was dry and coated with a white film. The swallowing reflex was impaired. Feeding was via a nasogastric tube. The second option was soft and non-tender. No fracture was detected. Urination was through the bladder. The stool was spontaneous and regular. Quality of life on the Karnofsky Performance Scale was 30%.

Local Findings: An ulcer was noted in the inguinal-occipital area, measuring 11.0×8.0 cm. Shape: round. Stage: III-IV. Inflammatory phase with a black scab. The wound edges were red and irregular. A foul odor and abundant

purulent discharge were present. Swelling. Painfullness. The wound bed was not visible.

The patient's daughter was angry, aggressive, and anxious. She answered questions angrily, briefly, and resentfully. According to the daughter, the patient knew the diagnosis but did not want to know the prognosis. The daughter was not willing to accept the severity and course of her mother's illness. She believed that the patient would be able to stand on her feet and walk.The patient's husband was also present during the examination.

Explanations were provided to establish a reliable connection. The assistance and actions of the mobile medical team were fully explained. Medical assistance was provided with the daughter's consent after completing the assessment. The pain level of the non-verbal patient was assessed using a special PAINAD scale.

Treatment:

Medical attention included:

1. IM administration of Analgin 50% (2.0 mL) + Ketatop (2.0 mL) and Dexamethasone (8 mg).

2. Bladder probe care, nasogastric tube care, and feeding skills were taught.

3. Conservative treatment of skin ulcers: washing with 0.05% chlorhexidine solution, 0.9% sodium chloride solution, actinosep, application of Oflomelid ointment and healing dressing, wound closure, and dressing securing.

4. All general and special care measures were performed.

Treatment prescribed: 1. Dexamethasone 4 mg – 1.0 intramuscularly once daily No. 10.

2. For mild pain – Ketop 2.0 + Analgin 50%-2.0 intramuscularly No. 1.

3. For night anxiety - Dimedrol 1% – 1.0 + Analgin 50% – 2.0 intramuscularly No. 1.

4. Consult a specialist in case of no stools for more than 3-4 days.

5. Relatives have been trained in nursing skills.

6. A functional bed, a special mattress to prevent skin ulcers in other areas, an electric medical suction for quality oral hygiene, and an oxygen concentrator to provide oxygen to the body are provided to ensure quality care.

7. A doctor visits depending on the severity of the patient's condition. Daily visits of a nurse or a nurse attendant. Psychologists and social workers' visits depending on the need.

The severity of the patient's condition, combined with her daughter's unstable psycho-emotional state, requires daily observation and comprehensive support. After the assistance was provided, the patient calmed down and foll asleep. The daughter calmed down considerably, though her anxiety and worry persisted.

The nurse conducted follow-up visits. The patient's condition remained extremely serious and required constant medical supervision and full care. The patient's daughter had consistently high levels of anxiety and irritability. She constantly protested and required the nurse to come and provide care before or after lunch, refusing to be present in the morning. In some cases, she completely refused care. The situation remained complex, given the severity of the patient's condition, the presence of extensive, complicated grade III-IV skin ulcers, and her daughter's unstable psycho-emotional state. It required constant monitoring, comprehensive medical care, and ongoing psychosocial support from all caregivers.

The next visit was performed by the head of the visiting team, a nurse, and a social worker (a team of women to create a comfortable environment for the relatives). The daughter continued to receive extremely negative, critical attitudes. The daughter was alone with her mother during the examination.

Neurological status: The level of consciousness – stupor. Meningeal symptoms – negative. Pupil OD=OS, photoreaction was lively. Nystagmus: none. Facial symmetry: Preserved. Right-sided hemiparesis. Numerical cognition cannot be assessed. According to the patient's daughter, she complained of frequent tremors in both upper and lower extremities. No vibrations were detected during the examination. During patient care, increased pain was observed during body movement, loud moaning, and restlessness. The pain was scored 4 on the PAINAD scale.

The situation was very serious. Breathing was even, spontaneous. Auscultation revealed equally diminished breath sounds on both sides. No wheezing was heard. Heart sounds were muffled, and tachycardia was present. Blood pressure: 90/60 mm Hg. Heart rate: 112 beats per minute. Oxygen saturation: 96%. The oxygen concentrator was often added. Body temperature: 37.8°C. The patient was motionless and required full assistance. The skin was pale and dry. No shortness of breath or coughing. The tongue was dry and clean. The swallowing reflex was impaired. The patient was fed via a nasogastric tube. The second option was soft and non-tender. No fracture was detected. Urination occurs through the bladder. The stool was spontaneous and regular. Quality of life on the Karnofsky Performance Scale – 30%.

Local Findings: An ulcer was noted in the inguinal-occipital area, measuring 11.0×8.0 cm. Shape: round. Stage: III-IV. Inflammatory phase with black scales. Wound edges are red and irregular. An unpleasant pungent odor and copious purulent discharge persisted. Swelling. Painfullness. The wound bed was not visible.

Medical assistance was provided after obtaining the daughter's consent and conducting a full assessment. Medical attention provided:

1. Suppression of pain and symptoms of hyperthermia.

2. Patient care. (Oral treatment, skin cleansing, washing, changing clothes and bed linen, etc.). All general and special care measures were performed.

3. Bladder probe care, nasogastric tube care, and feeding skills were taught.

3. Conservative treatment of skin ulcers: washing with 0.05% chlorhexidine solution, 0.9% sodium chloride solution, actinosep, application of Oflomelid ointment and healing dressing, wound closure, and dressing securing.

After the rendered help, the patient calmed down, and her body temperature was 36.2°C. the pain was scored 0 on the PAINAD scale.

Treatment prescribed: 1. Dexamethasone 4 mg – 1.0 intramuscularly once daily No. 10.

2. Tramadol 5% – 1.0 intramuscularly every 12 hours, regular, long term, under observation.

3. Carbamazepine 100 mg twice daily via a gastric tube or sublingually for a long time under observation.

2. For mild pain – Ketop 2.0 + Analgin 50% – 2.0 intramuscularly No. 1.

3. For night anxiety - Dimedrol 1% – 1.0 + Analgin 50% – 2.0 intramuscularly No. 1.

4. Consult a specialist if stools are absent for more than 3-4 days.

5. Relatives have been trained in nursing skills.

6. Relatives were trained in the proper use and care of the devices provided to improve the quality of patient care: functional bed, mattress, electric medical suction, and oxygen concentrator.

7. The doctor's appointment schedule depends on the severity of the patient's condition. Daily visits of a nurse. Psychologists and social workers' visits depending on the need.

During a conversation with the patient's daughter, it became clear that the cause of her intense anxiety and distress was not dissatisfaction with the medical care but rather her psycho-emotional state. In the course of the conversation, she spoke about her life, including the difficulties she experienced due to two failed marriages, her mother's current critical condition, and how it had significantly affected her overall emotional state.

She spoke of her mother's three marriages and her negative memories of her father. She mentioned that her mother's relationship with her third husband was difficult. Her mother lived separately from her husband until her condition deteriorated. After her mother's condition worsened, the daughter took both her mother and her husband into her home. The daughter does not like her mother's husband because all men remind her of her failed family life. For this reason, she shared that she experiences heightened anxiety when a nurse (a man) comes.

During the psychological intervention, the daughter cried for a long time and then said she began to feel better. She recalled that at first encounter with the mobile team, she could not fully open up because they were strangers to her, and she initially met them with distrust. "I met you with disapproval, but after seeing how you treat my mother, I changed my opinion and began to trust you." "However, if possible, I would prefer female staff to assist my mother," she said.

Results: A nurse (woman) performed the visits for a long time. As a result of the continuous provision of necessary medical care, quality nursing, and psychological and social support, the daughter's psycho-emotional state significantly improved. Pain symptoms were controlled, and the patient's condition was stable but serious. During care, the skin ulcer in the occipital region began to heal slowly. Her daughter fully mastered caregiving skills.

The patient was under the care of the mobile team for 2 months and 4 days. The daughter expressed her gratitude for the assistance provided to her mother and for helping her find peace and confidence.

Healing and recovery dynamics of skin ulcers with conservative treatment:

A skin ulcer measuring 11.0×8.0 cm in the occipital region. The shape – round. Stage: III-IV. Inflammatory phase with a black scab. Wound edges are red and irregular. A foul, pungent odor and abundant purulent discharge were present. Swelling. Painfullness. The wound bed was not visible.

Considering the severity of the patient's condition, conservative treatment was performed: the ulcer was treated with 0.05% chlorhexidine solution, 0.9% sodium chloride solution, actinosep, Oflomelid ointment was applied, the wound was sutured, and a bandage was applied. The treatment aimed to soften the necrotic hard black crust (Figure 1a).

A localized skin ulcer with dimensions of 11.0 × 8.0 cm was detected in the occipital region. The shape was round. Stage: III-IV. In the inflammatory phase, the black crust slightly decreased in size, and the wound edges became more distinct. The first fracture was slightly depressed. Unpleasant odor and copious purulent discharge have decreased. Pain persisted. The wound bed was not visible.

The conservative treatment was performed: the ulcer was washed with 0.05% chlorhexidine, 0.9% sodium chloride, and actinosep. A dressing with Oflomelid ointment was applied, the wound was sutured, and the dressing was fixed. The treatment aimed to soften the necrotic hard black crust (Figure 1b).

A localized skin ulcer with dimensions of 11.0 × 8.0 cm was detected in the occipital region. The shape was round. Stage: III-IV. In the inflammatory phase, the number of black scales significantly decreased, and the wound edges became clearer and more defined. The first fracture had healed. No unpleasant odor or purulent discharge was detected. The pain subsided. The wound bed was not yet fully visible.

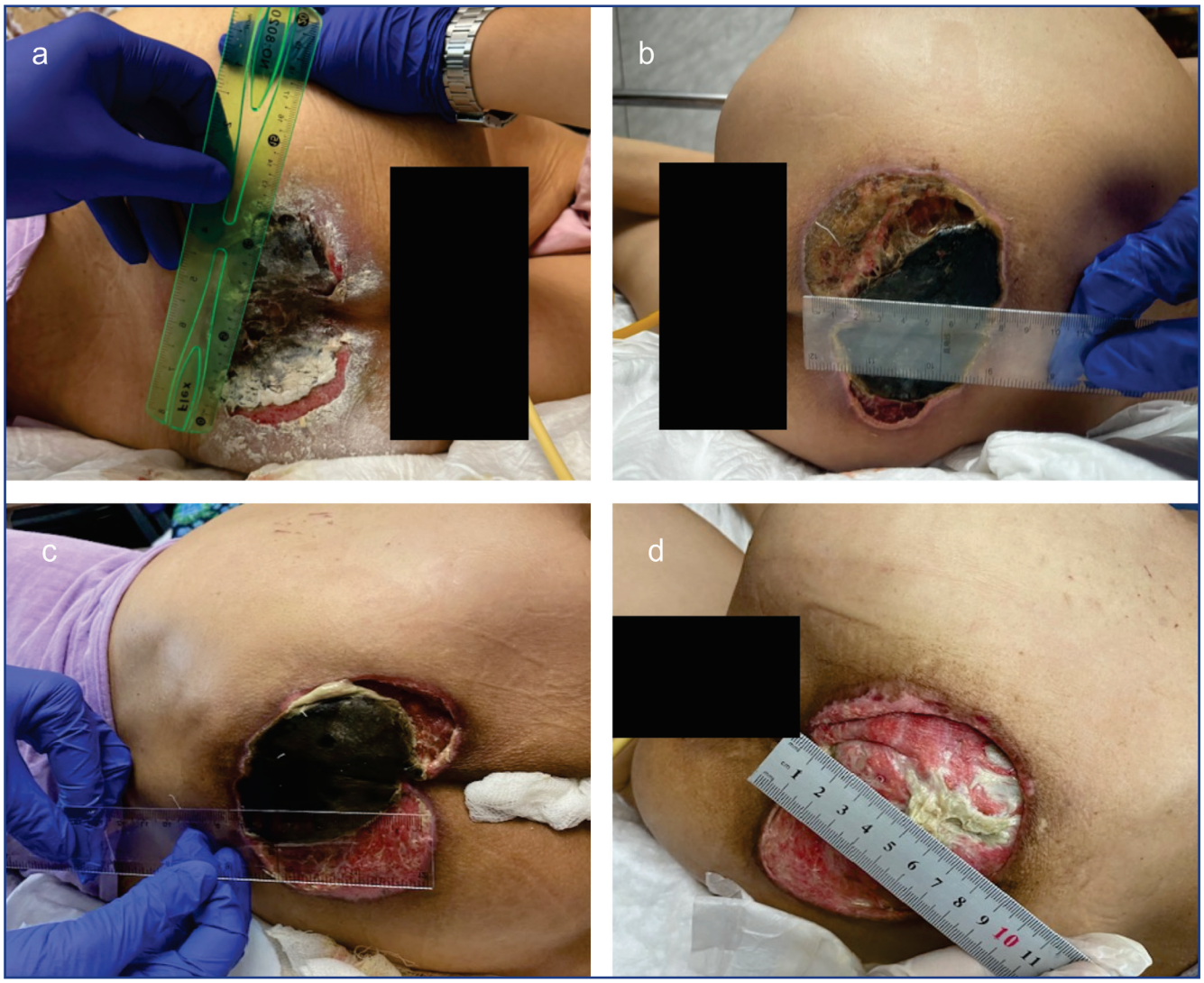

Figure 1 – Healing and recovery dynamics of skin ulcers with conservative treatment

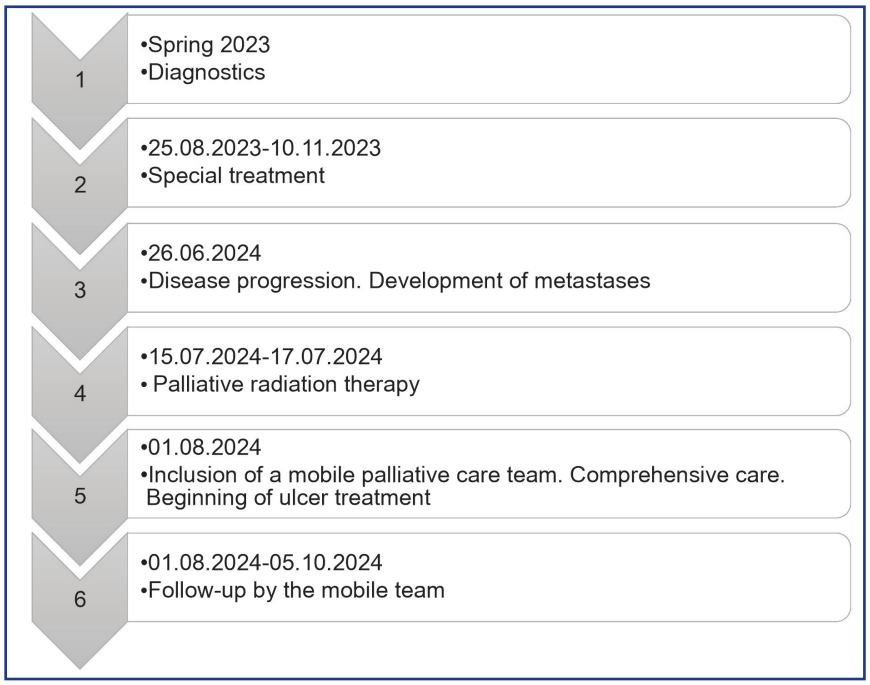

Figure 2 – Timeline of palliative care for a patient with metastatic breast cancer

Conservative treatment was performed: the ulcer was cleansed with a 10% betadine solution, necrotic black crusts were mechanically excised, and purulent cavities were opened. Baneocin ointment was applied, a healing dressing was placed over the wound, and the dressing was secured. The treatment aimed to soften and excise the necrotic hard black crust (Fig. 1c).

Locally, a skin ulcer measuring 10.0 × 7.0 cm in the occipital region was identified, which had progressed to the granulation phase. The shape was round. Stage: III-IV. The black crust has completely disappeared. No fractures are observed. The unpleasant odor and purulent discharge have completely resolved. No signs of pain are detected. No nook was present. The wound bed was fully visible. The wound edges are smooth, and granulation tissue formation is observed.

Conservative treatment was performed: the ulcer was cleansed with a 10% betadine solution, necrotic black crusts were mechanically excised, and purulent cavities were opened. Baneocin ointment was applied, a healing dressing was placed over the wound, and the dressing was secured. The treatment aimed to soften and excise the necrotic hard black crust (Fig. 1c).

Locally, a skin ulcer measuring 10.0 × 7.0 cm in the occipital region was identified, which had progressed to the granulation phase. The shape is round. Stage: III-IV. The black crust has completely disappeared. No fractures are observed. The unpleasant odor and purulent discharge have completely resolved. No signs of pain are detected. No nook is present. The wound bed is fully visible. The wound edges are smooth, and granulation tissue formation is observed.

Conservative treatment was provided: the ulcer was cleansed with a 0.9% sodium chloride solution and Octenisept. Foreign bodies and plaque were mechanically removed. A therapeutic dressing with methyluracil ointment was applied, the wound was sutured, and the dressing was secured. The treatment aimed to accelerate wound healing and recovery (Fig. 1d).

The timeline of the clinical case is presented in Figure 2.

Discussion: This clinical case of a patient with tumor-infiltrative breast cancer at stage III B illustrates the challenges associated with treating late-stage metastatic tumors. Disease progression, accompanied by metastases to the brain and pelvis and the development of degree III-IV skin ulcers, highlights the need for an interdisciplinary approach to optimize patient care and improve quality of life.

The tumor-infiltrative type of breast cancer is characterized by aggressive progression and a poor prognosis. Early diagnostics and targeted therapy based on HER2-positive status, as in this case, can slow disease progression and improve overall prognosis [7].

Treatment regimens containing docetaxel, trastuzumab, and pertuzumab are standard for HER2-positive breast cancer, although limited data suggest that their effectiveness diminishes in the very late stages of the disease [8, 9].

Particular attention was paid to treating degree III-IV skin ulcers that significantly deteriorate the patient's quality of life and increase the risk of infectious complications. Conservative treatment with ointments based on antibiotics and anti-inflammatory components, such as Oflomelid, has proven effective in reducing inflammation and softening necrotic hard crusts. The transition of the wound into the granulation phase after 1.5 months of treatment confirms the effectiveness of the chosen approach [10].

The work of the mobile palliative care team is a key component of care for terminal cancer patients at home. In this case, the cooperation of the physician, nurse, psychologist, and social worker not only provided the patient with the necessary care but also helped stabilize the emotional state of the patient's family members, which directly affects patient satisfaction with care outcomes and quality of life [11]. Effective communication between team members and patients' relatives helps reduce stress and aggression, which is especially important in families with a tense psychological environment [12, 13].

The mobile team's specialists also played an essential role in training the patient's relatives in caregiving skills. Step-by-step instruction, support, and regular monitoring ensured the correct implementation of all necessary procedures, including skin ulcer treatment care for the nasogastric tube and urinary catheter, contributing to a significant improvement in the condition of the skin ulcers and a reduction in complications. This emphasizes the importance of medical intervention and social support as part of palliative care [14, 15].

Conclusion: This case demonstrates that an interdisciplinary approach can achieve optimal outcomes even in complex clinical situations. The involvement of a team of specialists, modern care protocols, and attention to the emotional needs of the patient and their family are essential to successful palliative care. Skin ulcer healing is a long-term process. Unfortunately, terminally ill patients often do not live to see the complete resolution of the ulcerative condition. However, the outcomes of the care provided can significantly improve the patient's quality of life.

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АНДАТПА

МЕТАСТАЗДЫ ЗАҚЫМДАЛУМЕН СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІ ДИАГНОЗЫМЕН НАУҚАСҚА МОБИЛЬДІ ТОПТЫҢ ҮЙ ЖАҒДАЙЫНДА ПАЛЛИАТИВТІ КӨМЕГІ: КЛИНИ-КЛЫҚ ЖАҒДАЙ

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Өзектілігі: *Паллиативті көмектің мақсаты ауырсыну және науқас жағдайын нашарлататын басқа да клиникалық белгілерді сауатты диагностикалап тиімді емдеу, науқас күтімі және туыстарына күтім дағдыларын үйрету, науқас және отбасына психологиялық, әлеуметтік қолдау.*

Зерттеу мақсаты *– метастатикалық зақымдануы бар-ісікті-инфильтративті сүт безі обыры диагнозы қойылған науқасқа үй жағдайында кешенді паллиативтік көмек көрсететін мобильді топтың рөлін зерттеу.*

Әдістері: *Мақалада бас миының, жамбас сүйектерінің метастаздармен зақымдалуы және III-IV дәрежелі терінің ойық жарасының дамуымен асқынған III В сатыдағы сүт безі қатерлі ісікті-инфильтративті түрі диагнозымен науқастың клиникалық жағдайы келтірілген. 4 цикл неоадъювантты полихимиотерапия және 4 цикл таргетті терапияның жүргізілгеніне қарамастан, үрдістің үдеуі. Науқас және оның отбасына үй жағдайында паллиативті кешенді медициналық және психологиялық, әлеуметтік қолдау көрсеткен мобильді топ жұмысына ерекше назар аударылады. Паллиативті көмектің негігі аспектілері ауырсыну белігілерін сауатты диагностикалап, нәтижелі емдеу.Төсек ойық жарасының күтімі, емі, назогастральды түтік арқылы тамақтануды, сондай-ақ эмоционалды шиеленісті азайту үшін туыстарымен өзара әрекеттесуді қамтыды.*

Нәтижелері: *III-IV дәрежелі терінің ойық жарасын емдеу нәтижелері оң динамиканы көрсетті, жараның 1,5 айға созылған консервативті емнен кейін грануляция фазасына ауысуы. Жараларды емдеудің заманауи әдістерін, соның ішінде антисептикалық ерітінділер мен антибиотикалық майларды қолдану инфекциялық асқынуларды азайтуға және науқастың жағдайын жақсартуға мүмкіндік берді. Мобильді топтың жұмысы паллиативтік көмек шеңберінде медициналық ғана емес, әлеуметтік қолдауды да қамтитын жеке көзқарастың маңыздылығын атап өтті.*

Қорытынды: *Мақала онкологиялық аурудың терминальды сатысындағы ауыр науқастарға үй жағдайында паллиативті көмек беру мобильді тобының қызметі науқастардың өмір сүру сапасын жақсарта отырып, көрсетілген көмекке қанағаттанушылығын арттыруға ықпал ететіндігін атап көрсетеді.*

Түйінді сөздер: *сүт безі қатерлі ісігі, ісікті-инфильтративті түрі, паллиативтік көмек, мобильді топ, терінің ойық жараларын емдеу, метастаздар, өмір сүру сапасы.*

АННОТАЦИЯ

ПАЛЛИАТИВНАЯ ПОМОЩЬ МОБИЛЬНОЙ БРИГАДЫ ПАЦИЕНТУ С МЕТАСТАТИЧЕСКИМ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Цель паллиативной помощи – грамотная диагностика и эффективное лечение боли и других тяжелых симптомов, ухудшающих состояние пациента, уход за больным и обучение родственников навыкам ухода, оказание психологической и социальной поддержки пациенту и его семье.*

Цель исследования *– изучить роль мобильной бригады в оказании комплексной паллиативной помощи на дому пациенту с диагнозом отечно-инфильтративного рака молочной железы с метастатическим поражением.*

Методы: *В статье представлен клинический случай пациента с диагнозом отечно-инфильтративной формы рака молочной железы стадии III В, осложнённого метастазами в головной мозг, тазовые кости и развитием пролежней III-IV степени. Несмотря на проведение 4 циклов неоадъювантной полихимиотерапии и 4 циклов таргетной терапии, процесс прогрессировал. Особое внимание уделено работе мобильной бригады, оказывающей комплексную медицинскую, психологическую и социальную поддержку пациенту и его семье в домашних условиях. Основные аспекты паллиативной помощи включали грамотное выявление и эффективное лечение болевых симптомов, уход и лечение пролежней, питание через назогастральный зонд, а также взаимодействие с родственниками для уменьшения эмоционального напряжения.*

Результаты: *Результаты лечения пролежней III-IV степени продемонстрировали положительную динамику: переход раны в фазу грануляции спустя 1,5 месяца консервативного лечения. Применение современных методов лечения ран, включая антисептические растворы и антибиотиковые мази, позволило снизить риск инфекционных осложнений и улучшить состояние пациента. Работа мобильной бригады подчеркнула важность индивидуального подхода, включающего не только медицинскую, но и социальную поддержку в рамках паллиативной помощи.*

Заключение: *Деятельность мобильных бригад, оказывающих паллиативную помощь тяжёлым онкологическим пациентам на терминальной стадии в домашних условиях, способствует улучшению качества жизни пациентов и повышению удовлетворённости получаемой помощи.*

Ключевые слова: *рак молочной железы, опухолево-инфильтративная форма, паллиативная помощь, мобильная группа, лечение пролежней, метастазы, качество жизни.*

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SGLT2-RECEPTOR INHIBITORS-ASSOCIATED EUGLYCEMIC DIABETIC KETOACIDOSIS IN ONCOSURGICAL PATIENTS IN THE EARLY POSTOPERATIVE PERIOD: A CASE REPORT

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АННОТАЦИЯ

Relevance: *Administration of SGLT2-receptor inhibitors in oncosurgical patients with diabetes mellitus could lead to a formidable complication – the development of euglycemic diabetic ketoacidosis (EDKA) – a specific condition that is difficult to diagnose in a wide range of specialists. The lack of information about this complication and, thus, vigilance due to normal glucose levels complicates early detection of EDCA in surgical patients. Regarding oncosurgical patients, data on the prevalence of SGLT2-associated EDCA in the early postoperative period is limited. The presented clinical case highlights the significant risks of intraoperative surgical stress and prolonged fasting in patients on SGLT2 inhibitor therapy, as well as the difficulties in timely recognition of this condition.*

This paper aimed to *increase the alertness and raise the awareness of clinical specialists about the risk of EDCA development in oncosurgical patients after the administration of SGLT2 inhibitors in the early postoperative period, the importance of timely diagnosis of this condition, and the ways of its treatment, using the example of the described clinical case.*

Methods: *The article describes a clinical case of an oncosurgical patient who developed EDKA in the early postoperative period as a complication of SGLT2 inhibitors administration.*

Results: *In the early postoperative period following the administration of dapagliflozin, the patient developed EDKA, which was successfully managed through adequate hydration with balanced crystalloid solutions, correction of glycemia with intravenous insulin infusion and 10% glucose solutions, and the correction of acid-base and blood electrolytes balance.*

Conclusion: *This clinical case demonstrates the importance of early diagnosis and treatment of EDCA as a rare but dangerous complication of SGLT2 inhibitors in oncosurgical patients.*

Keywords: *euglycemic diabetic ketoacidosis (EDKA), SGLT2 inhibitors, Dapagliflozin.*

Introduction: SGLT2 inhibitors represent a new generation of oral antihyperglycemic agents for treating type 2 diabetes mellitus (T2DM). These medications lower blood glucose levels by inhibiting glucose reabsorption in the proximal renal tubules, thereby promoting glucosuria [1]. They are often preferred due to their cardiovascular and renal protective effects; however, their use has been associated with certain metabolic complications [2]. The most notable – though rare – of these is euglycemic diabetic ketoacidosis (EDKA), a condition that occurs with normal or near-normal blood glucose levels (<13.8 mmol/L or 250 mg/dL). EDKA arises from increased ketone production due to enhanced lipolysis and decreased insulin secretion, typically due to insufficient carbohydrate intake [3]. A similar condition, known as "starvation ketosis," is well-documented in non-diabetic patients. However, this form of ketoacidosis is atypical in diabetes, and normal blood glucose levels can delay diagnosis, leading to an increased risk of metabolic complications [4]. A particularly vulnerable subgroup includes oncology patients with diabetes who are undergoing surgical procedures. The postoperative period is characterized by numerous metabolic stressors, such as fasting, insulin resistance, and surgical stress responses, all of which can accelerate the onset of EDKA in patients taking SGLT2 inhibitors. Delayed recognition of this condition can lead to serious complications, including metabolic acidosis and hemodynamic instability [5]. Therefore, prevention, early detection, and timely management of this complication are crucial to improving patient outcomes [6].

Materials and methods: This article presents a case of euglycemic diabetic ketoacidosis (EDKA) in the early postoperative period in a patient of uro-oncological profile receiving SGLT2 inhibitor therapy. The patient was hospitalized at the Kazakh Institute of Oncology and Radiology (KazIOR), Almaty, Kazakhstan, in 2025. The patient provided signed informed consent for all procedures, as well as for the use of treatment outcomes

for scientific research, educational, academic, and promotional purposes.

Clinical case:

Patient Information: Patient D., a 56-year-old male, was admitted on a scheduled basis with a diagnosis of stage 1 bladder cancer (C-r of the bladder, stage 1). Comorbidities included: Grade 1 arterial hypertension, risk level 4 Type 2 diabetes mellitus (T2DM). The patient was scheduled to undergo transurethral resection of the bladder (TURB). Medical History: The patient had been followed by an endocrinologist for over 10 years for T2DM. Over the past year, he had been taking dapagliflozin (an SGLT2 inhibitor) at a dose of 10 mg/day. An endocrinologist who examined the patient during the pre-hospital phase identified no contraindications to surgery. An outpatient preoperative anesthesiology assessment was conducted at the polyclinic of KazIOR JSC (Almaty, Kazakhstan). The anesthesiologist recommended discontinuing dapagliflozin 72 hours (3 days) prior to surgery. A repeat evaluation was performed after hospital admission, one day before surgery. The anesthesiologist advised the attending physician to monitor and manage glycemic control and fluid balance. The surgical procedure was uneventful, lasting 50 minutes, and was performed under regional anesthesia – spinal anesthesia at the L3 - L4 level using a 27G needle, with 5 mL of 0.5% Bupivacaine Spinal solution.

Clinical Data: Laboratory tests conducted the day before admission revealed blood glucose of 13.5 mmol/L; other parameters were within normal limits. Only 500 mL of a balanced electrolyte solution was administered intravenously during surgery. No intraoperative blood glucose monitoring was performed. Postoperative observation in the recovery room was uneventful, and the patient was transferred to the specialty ward. The next day, routine tests showed 5.8 mmol/L of blood glucose. in the urinalysis, ketonuria was (++) and glucosuria (+). These findings were initially interpreted as a reaction to preoperative fasting. However, the patient's clinical condition deteriorated, with emerging signs of decompensated diabetes, and by the following morning, he was transferred to the intensive care unit (ICU). Further evaluation revealed severe metabolic acidosis, high anion gap due to ketones (28 mEq/L), normal blood glucose (6.4 mmol/L), normal lactate levels, significant glucosuria (++), and marked ketonuria (++++) (Table 1).

Table 1 – Laboratory Tests During Hospitalization

Hospitalization Day	Day 0	TURB* Surgery	Postoperative Day 1	ICU** Day 1	ICU Day 2	ICU Day 3
pH				7.11	7.29	7.41
Glucose (mmol/L)	13.5		5.8	6.4	11.6	5.9
HCO_3				7.6	24.3	29
pCO_2				12.9	46	44.3
Anion Gap				28	10	8
BE***				-24.9	1.3	5.9
Lactate				1.0	0.7	0.6
Ketonuria	abs.	++	+++	++++	+/-	abs.
Glucosuria	abs.	+	++	++	abs.	abs.

*Notes: *TURB – Transurethral Resection of the Bladder; **ICU – Intensive Care Unit; ***BE – Base Excess*

Diagnostics: Initially, the development of ketoacidosis was attributed to hypovolemia, but the patient showed no response to fluid resuscitation. It was further revealed that the patient had consumed almost no food since admission due to a poor appetite, had not maintained proper hydration, and his diabetes was being managed with insulin based on glucose levels alone, without carbohydrate supplementation. This combination of clinical information and laboratory findings led to the suspicion of euglycemic diabetic ketoacidosis (EDKA) in the context of ongoing SGLT2 inhibitor therapy.

Treatment: The patient was started on adequate intravenous fluid therapy using balanced crystalloids, and a continuous intravenous insulin infusion was initiated at a starting dose of 0.1 IU/kg/day. Glycemic levels were closely monitored and corrected accordingly, with a 10% glucose infusion to prevent hypoglycemia. Ongoing monitoring included acid-base balance and electrolyte levels.

Results: Ketoacidosis resolved within 48 hours (see dynamics in Table 1). The patient was subsequently switched to a subcutaneous insulin regimen. No recurrence of EDKA occurred during the remainder of the hospital stay.

The timeline of the clinical case is presented in Table 2.

Table 2 – Clinical Timeline of EDKA in a Uro-oncological Patient on SGLT2 Inhibitor Therapy

Date	Event	Note
14.01.2025	Pre-hospital endocrinology consultation	Type 2 diabetes diagnosed; no contraindications for surgery
17.01.2025	Outpatient preoperative anesthesiology assessment	The patient underwent an anesthesiology consultation, during which discontinuation of dapagliflozin was advised
20.01.2025	Admission – Day 1 of planned hospitalization	Repeat anesthesiology evaluation; 2.5 days since dapagliflozin withdrawal
21.01.2025	TURB* surgery	Duration: 50 minutes Anesthesia: SA**
22.01.2025	Postoperative care in specialty ward	
23.01.2025	Transferred to ICU*** with signs of DM^ decompensation	ICU*** Day 1 - Intensive therapy and monitoring initiated
24.01.2025	ICU*** Day 2	Ongoing intensive care, continuous monitoring, and correction of acid-base status and glycemic control
25.01.2025	ICU*** Day 3	Clinical stabilization; resolution of ketoacidosis; transfer to a ward for further treatment
01.02.2025	Patient discharged	

*Notes: *TURB – Transurethral Resection of the Bladder; **SA – Spinal Anesthesia; ***ICU – Intensive Care Unit; ^DM – Diabetes Mellitus*

Discussion: SGLT2 receptor inhibitors (gliflozins) act on mechanisms in the proximal renal tubules responsible for reabsorbing filtered sodium and glucose. Clinically, this results in reduced blood glucose levels and increased urinary sodium excretion. These agents are widely used for glycemic control in diabetes, reducing cardiovascular event risk in diabetic patients, and treating heart failure. However, alongside their benefits, SGLT2 inhibitors carry risks, including genitourinary infections, acute kidney injury, skeletal fractures, and, notably, ketoacidosis at relatively normal blood glucose levels [7]. Their use also increases perioperative risks, as documented in multiple case reports of EDKA in surgical patients, highlighting the importance of recognizing this class of hypoglycemic agents as a potential perioperative risk factor [8]. In a prospective study involving 759 surgical patients, the incidence of postoperative SGLT2i-induced ketoacidosis was 0% (95% CI: 0 - 0.4%) [9]. Case reports have documented instances of EDKA occurring in the postoperative period. For example, a 58-year-old woman developed EDKA 48 hours after her last dose of empagliflozin and one day post-neurosurgery [10]. In a broader context, a study involving cardiac surgery patients reported a 70.8% incidence of ketoacidosis associated with SGLT2 inhibitor use [11]. However, this high rate may not be directly extrapolatable to populations undergoing cancer surgery due to differing patient characteristics and responses to surgical stress.

Patients undergoing bowel preparation prior to surgery, as well as cancer patients, are often subject to prolonged periods of reduced caloric intake. This can lead to energy depletion and dehydration, particularly when combined with SGLT2 inhibitor therapy. These factors may contribute to the development of EDKA even before the onset of surgical stress [7]. The perioperative period is marked by various physiological disturbances, including dehydration due to fasting, restricted intake, and increased metabolic demand following surgery, all of which favor ketosis. Moreover, surgical stress triggers a catecholamine surge, stimulating gluconeogenesis, lipolysis, and ketogenesis [12]. A normal blood glucose level may mask the onset of EDKA, complicating its early detection. Therefore, clinicians must maintain a high index of suspicion for EDKA in patients on SGLT2 inhibitors [13]. Pre- and postoperative fasting and stress-induced metabolic shifts further exacerbate the ketogenic potential of SGLT2 inhibitors [14]. According to the literature, preoperative discontinuation of SGLT2 inhibitors and careful perioperative monitoring can reduce the risk of developing EDKA; however, the optimal duration of drug withdrawal remains a matter of debate [6]. Current updated guidelines suggest withholding SGLT2 inhibitors for 3-4 days prior to scheduled surgery [7].

Intraoperative management in diabetic patients also requires attention: glucose monitoring, administration of glucose-containing solutions, and insulin therapy are crucial [8].

Continuous blood gas monitoring is essential for early identification and correction of metabolic acidosis. Nutritional support, including adequate carbohydrate intake, is advised to reduce postoperative ketone production [15]. Fluid resuscitation, insulin therapy, and careful ketone monitoring are the cornerstones of both the prevention and management of EDKA in postoperative patients [16]. Educating patients and healthcare providers on early EDKA symptoms — such as nausea, fatigue, and abdominal pain — is vital for timely intervention [4]. Skilled endocrinology consultation in the perioperative setting is crucial for patients on SGLT2 inhibitors undergoing surgery, facilitating prevention, early detection, and appropriate management [8]. A multidisciplinary perioperative ap-

proach involving endocrinologists, anesthesiologists, and surgeons is essential to minimize the risk of this potentially life-threatening complication [17].

Conclusion: The presented clinical case highlights the importance of recognizing EDKA as a potential complication associated with using and discontinuing SGLT2 inhibitors in the days leading up to surgery and during the early postoperative period. It is essential to provide patients with low-dose insulin and carbohydrate support during surgery to suppress ketogenesis, along with close monitoring of laboratory parameters to minimize the risk of EDKA, which can significantly complicate postoperative recovery.

There is a clear need to develop standardized perioperative management protocols for patients with diabetes who are taking SGLT2 inhibitors in order to reduce the risk of EDKA while preserving the therapeutic benefits of these agents in diabetes care. Physician education and patient awareness may also be crucial in preventing or mitigating the consequences of this potentially serious complication.

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АҢДАТПА

ОПЕРАЦИЯДАН КЕЙІНГІ ЕРТЕ КЕЗЕҢДЕ ОНКОХИРУРГИЯЛЫҚ БЕЙІНДЕГІ ПАЦИЕНТТЕРДЕ SGLT2-РЕЦЕПТОРЛАР ИНГИБИТОРЛАРЫМЕН ЕМДЕУ АЯСЫНДА ЭУГЛИКЕМИЯЛЫҚ ДИАБЕТТІК КЕТОАЦИДОЗ: КЛИНИКАЛЫҚ ЖАҒДАЙ

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Өзектілігі: *қант диабетімен ауыратын онкологиялық науқастарға SGLT2 рецепторларының ингибиторларын енгізу ауыр асқынуларға әкелуі мүмкін-эвгликемиялық диабеттік кетоацидоздың (EDKA) дамуы - көптеген мамандарда диагноз*

қою қиын болатын ерекше жағдай. Мұндай асқыну туралы ақпараттың болмауы және сәйкесінше глюкозаның қалыпты деңгейіне байланысты сергектік хирургиялық науқастарда ЭДКА-ны ерте анықтауды қиындатады. Операциядан кейінгі ерте кезеңдегі онкологиялық науқастардың контекстінде SGLT2-мен байланысты EDCA таралуы туралы деректер шектеулі. Біздің клиникалық жағдайымыз SGLT2 ингибиторлық терапиясын қабылдаған емделушілерде операция ішілік хирургиялық стресстің және ұзақ уақыт ораза ұстаудың елеулі қауіптерін, сондай-ақ бұл жағдайды уақтылы танудағы қиындықтарды көрсетеді.

Зерттеудің мақсаты: *SGLT2 тежегіштерін енгізумен байланысты операциядан кейінгі ерте кезеңде онкологиялық науқастарда EDCA даму қаупі туралы клиникалық мамандардың қырағылығы мен хабардарлығын арттыру; осы жағдайды уақтылы диагностикалаудың маңыздылығы, сондай-ақ осы клиникалық жағдай мысалында оны емдеу жолдарын зерттеу.*

Әдістері: *Мақалада операциядан кейінгі ерте КЕЗЕҢДЕ ЭДКА дамыған онкологиялық науқастың клиникалық жағдайы SGLT2 тежегіштерін енгізудің асқынуы ретінде сипатталған.*

Нәтижелері: *Операциядан кейінгі ерте кезеңде дапаглифлозинді қабылдағаннан кейін науқасқа ЕДКА диагнозы қойылды, содан кейін ол теңдестірілген кристаллоидты ерітінділермен адекватты гидратациямен, ішілік инсулинмен және 10% глюкоза ерітіндісімен гликемияны түзетумен, қышқыл-негіз балансын және қан электролиттерін түзету арқылы сәтті емделді.*

Қорытынды: *Біздің клиникалық жағдайымыз онкохирургиялық науқастарда SGLT2 тежегіштерінің сирек, бірақ қауіпті асқынуы ретінде EDCA-ны ерте диагностикалау мен емдеудің маңыздылығын көрсетеді.*

Түйінді сөздер: *эвгликемиялық диабеттік кетоацидоз (ЭДКА), SGLT2 ингибиторлары, Дапаглифлозин.*

АННОТАЦИЯ

ЭУГЛИКЕМИЧЕСКИЙ ДИАБЕТИЧЕСКИЙ КЕТОАЦИДОЗ НА ФОНЕ ТЕРАПИИ ИНГИБИТОРАМИ SGLT2-РЕЦЕПТОРОВ У ПАЦИЕНТОВ ОНКОХИРУРГИЧЕСКОГО ПРОФИЛЯ В РАННЕМ ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Прием ингибиторов SGLT2-рецепторов у пациентов онкохирургических профилей с сахарным диабетом 2 типа может сопровождаться грозным осложнением – развитием эугликемического диабетического кетоацидоза (ЭДКА). Данное специфическое осложнение вызывает трудности в диагностике у многих специалистов. Недостаточная информированность о таком осложнении и, соответственно, отсутствие настороженности из-за нормального уровня глюкозы затрудняет раннее выявление ЭДКА у хирургических пациентов. В отношении онкохирургических пациентов данные о распространенности SGLT2-ассоциированного ЭДКА в раннем послеоперационном периоде ограничены. Представленный клинический случай дополняет объем сведений, подчеркивающих значительные риски, возникающие при интраоперационном хирургическом стрессе и длительном голодании у пациентов с терапией ингибиторами SGLT2, а также трудности своевременного распознавания данного состояния.*

Цель исследования *– повышение настороженности и информированности клинических специалистов о риске развития ЭДКА у онкохирургических пациентов на фоне приема ингибиторов SGLT2 в раннем послеоперационном периоде, важности своевременного диагностирования данного состояния, а также способах его лечения на примере данного клинического случая.*

Методы: *В статье описан случай ЭДКА у пациента онкохирургического профиля в раннем послеоперационном периоде на фоне приема ингибиторов SGLT2.*

Результаты: *В раннем послеоперационном периоде после приема препарата Дапаглифлозин у пациента был диагностирован ЭДКА, который был успешно купирован с помощью адекватной гидратации сбалансированными кристаллоидными растворами, коррекции гликемии внутривенной инфузией инсулина и растворов глюкозы 10%, коррекции кислотно-щелочного баланса и электролитов крови.*

Заключение: *Данный случай демонстрирует важность своевременной диагностики и коррекции ЭДКА как редкого, но опасного осложнения приема ингибиторов SGLT2 у пациентов онкохирургического профиля.*

Ключевые слова: *эугликемический диабетический кетоацидоз (ЭДКА), ингибиторы SGLT2, Дапаглифлозин.*

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MODERN METHODS OF MALIGNANT SKIN MELANOMA EARLY DETECTION: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Skin melanoma is the most dangerous malignant neoplasm of the skin; it ranks ninth in the structure of oncological diseases worldwide. Despite the simplicity of preventive measures and the fact that melanoma is one of the most visually detectable tumors, its incidence continues to rise globally each year. As a result, enhancing early detection and prevention strategies remains a critical public health priority. Dermatoscopy remains the gold standard for early diagnosis, serving as the foundation for all modern diagnostic equipment. Additionally, specialized genetic testing methods are available to identify familial melanoma cases in high-incidence regions.*

The study aimed to *describe the capacity of modern early skin melanoma detection methods.*

Methods: *We used specialized scientific search engines such as Scopus and PubMed to examine current methods for early melanoma skin cancer detection described in publications from 2014 to 2024.*

Results: *Dermatoscopy and confocal microscopy remain the first choices for specialized physicians due to their simplicity and accessibility. Although Nevisense electrical impedance spectroscopy has a high diagnostic value, it is inaccessible to patients and physicians. AI-based mobile dermatoscopic applications are promising because they are accessible to both parties. CDKN2A genetic testing is used in regions with a high population incidence of melanoma to detect familial malignant melanoma syndrome.*

Conclusion: *Further technological progress shall promote modern methods of diagnosing skin melanoma based on efficiency, cost-effectiveness, simplicity, and accessibility.*

Keywords: *malignant skin melanoma, early detection, noninvasive methods, familial melanoma.*

Introduction: Malignant skin melanoma (MSM) is a serious type of skin cancer that develops from melanocyte cells. Although squamous cell carcinoma is less common than basal cell carcinoma and squamous cell carcinoma, which originate from epithelial tissue, it is considered dangerous due to its ability to rapidly metastasize to other organs [1]. Melanocytes are skin cells located in the upper layer of the skin. They produce the pigment melanin, which gives the skin its color. There are two types of melanin: eumelanin and pheomelanin. When the skin is exposed to ultraviolet radiation from the sun or artificial tanning, it causes damage to the skin. As a result, melanocytes produce more melanin, which protects the eumelanin pigment from the skin, causing it to darken or tan. Modern oncology views MSM proliferation as a complex multifactorial process with a combination of genetic, epigenetic, and environmental factors that contribute to its occurrence and can be prevented [2]. MSM occurs when DNA damage by UV radiation caused by sunburn or oxidation induces mutations in melanocytes, which triggers a complex mechanism of uncontrolled cell growth. International Agency for Research on Cancer has classified solar ultraviolet radiation and tanning devices that emit artificial ultraviolet radiation as carcinogens, placing them in the highest risk category for colon cancer, alongside other carcinogens such as radon, tobacco, and asbestos. Solarium-induced melanoma affects more people than lung cancer caused by smoking [3]. According to the International Agency for Research on Cancer (Lyon, France), 325,000 cases of melanoma (174,000 cases in men, 151,000 cases in women) were reported worldwide in 2020, and 57,000 people (32,000 men and 25,000 women) died from it [4]. One important factor in the incidence of MSM is geographical location. The incidence of MSM is highest in equatorial regions and decreases as one moves north or south of the equator, which is related to the number of hours of sunlight in these regions compared to regions of greater or lesser longitude [5]. The incidence of colorectal cancer has increased worldwide, not only in the last decade but also in the past, and this increase is faster than other cancers [6]. The most alarming element of these statistics is the relatively young age of patients suffering from MSM. Unlike colorectal (68 years), lung (70 years), and prostate (71 years) cancers, the median age of diagnostics in patients with MSM is only 57 years.

The study aimed to describe the capacity of modern early skin melanoma detection methods.

Materials and methods: Data were collected from peer-reviewed sources indexed in the scientific search systems Scopus and PubMed between 2014 and 2024. A total of 48 sources were retrieved based on the keywords of the study. We also analyzed open-access articles from the European Consensus Interdisciplinary Guidelines for Melanoma Research. Of these, 15 sources were included in the analysis, providing an overview of current STI prevention methods.

Results:

Dermatoscopy and confocal microscopy. Dermatoscopy is the most common, simple, and accessible method of early diagnostics. Dermatoscopy has been shown to have a diagnostic accuracy of up to 89% compared with clinical diagnostics of skin lesions [7]. Dermatoscopy should be used for all malignant skin neoplasms, not just for clinical suspicion. This is because dermatoscopy allows the detection of morphologic asymmetry of MSM before it is clinically recognized. Dermatoscopic photodocumentation of the lesion before surgical removal is primarily recommended [8]. Dermatoscopic features of MSM are distinguished using the CASH algorithm (C-color, A-architecture, S-symmetry vs. asymmetry, H-homogeneity vs. heterogeneity), an improved version of the ABCD algorithm. These include color polychromy, irregular arrangement of structures in the dermatoscopic image, symmetry and asymmetry of patterns, and the presence of the following dermatoscopic appendages: atypical pigmented mesh, irregular brown-black dots/balls, irregular stripes and lines, white shiny stripes, "blue-white veil" feature, and polymorphic veins. Figure 1 shows the dermatoscopic image of MSM according to the clinical presentation: A - MSM on the face resembling a brown flat pigmented lesion, and dermatoscopy shows a brown pseudo grid with irregular pigmentation of follicular openings; B - Dermatoscopic image of superficially distributed MSM with brown asymmetry on the body skin shows color asymmetry, atypical globules, and pigmented mesh; C - Nodular melanoma of the body skin with a bluish hue, whose dermatoscopic image shows bluish pink color and asymmetry of structures, globules and polymorphic vessels, and white streaks. Confocal microscopy provides images of the epidermis and superficial layer of the dermis. Like dermatoscopy, it allows the evaluation of pathologic changes in skin tissue by obtaining images in the horizontal plane. In confocal microscopy, the contrast image is obtained due to differences in the refractive index of the laser beam of organelles and other cellular microstructures, which appear lighter against the background of underlying structures. Confocal microscopy is a promising practical tool for diagnosing and monitoring pigmented and non-pigmented skin neoplasms. It shows horizontal skin layers with a maximum depth of 350 μm. When examining the skin, the resolution provided by confocal microscopy is very important compared to histologic examination since lateral resolution is less than 1 μm, and vertical resolution is 3 to 5 μm.

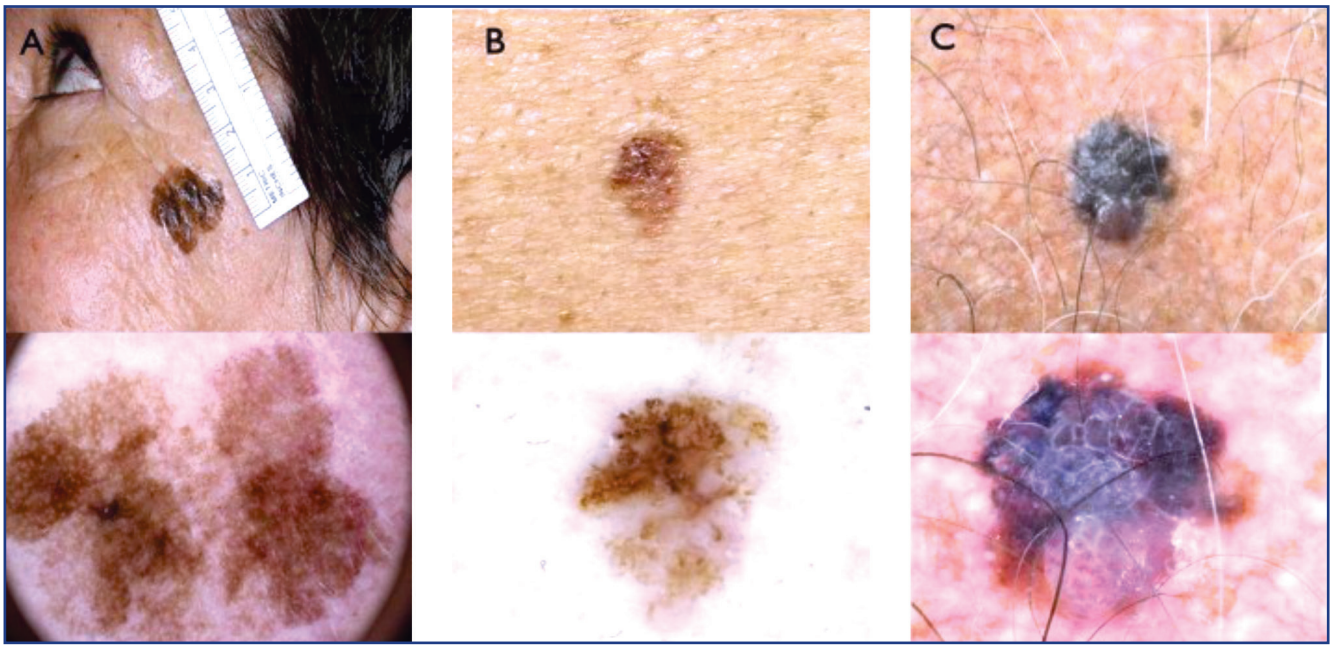

Figure 1 - Clinical and dermatoscopic picture of malignant skin melanoma

Electrical Impedance Spectroscopy. This method analyzes the electrical resistance or conductivity of materials and systems at various frequencies. The Nevisense system, which analyzes with this method, determines the degree of conductivity of skin neoplasms by passing electrical currents of different frequencies through a device similar to an ultrasound probe. Since MSM cells conduct electric current more actively and faster than healthy skin cells, this effect can be registered using spectroscopy based on electrical resistance measurements [9, 10]. Thanks to pre-established control measurements, the system allows for comparing CT scan results with measurements from the lesion area on the skin of the intended patient. In an international multicenter prospective study conducted at 5 U.S. and 17 European research centers, 256 of 265 cases of histologically confirmed squamous cell cancer were preliminarily identified by the Nevisense system using electrical impedance spectroscopy with an accuracy of 96.6% and an accuracy of 100% for non-melanoma skin cancer. Thus, the Nevisense system can be a noninvasive method for screening colorectal cancer in high-incidence countries [11, 12].

Artificial intelligence (AI) technology based on dermatoscopic applications for mobile phones. AI-based mobile applications are a simple, practical, and accurate diag-

nostics method for suspected skin cancer and squamous cell carcinoma in patients visiting oncological dermatologists. However, its use requires careful refinement of the decision-making mechanisms within the program [13]. Most retrospective studies in oncodermatology show a clear advantage of AI over humans [14]. The International Skin Imaging Collaboration 2018 Challenge study compared 10,015 computer algorithms across 7 diagnoses (MSM, nevus, dermatofibroma, pigmented basal cell carcinoma, non-pigmented basal cell carcinoma, keratosis, and benign vascular tumors). The ISIC 2018 AI algorithms were more accurate than the diagnoses of young specialists. However, the study, like almost all studies of this type, was not conducted in realistic everyday clinical settings; Instead, physicians were forced to evaluate images on a computer screen without contextual information. Thus, it remains unclear whether the benefits of IA obtained in this study will be implemented in clinical practice. The results of the ACTRN12620000695909 multicenter prospective diagnostic clinical trial conducted in Australia and New Zealand, which allowed real-time validation of the ISIC 2018 study, are described as a "new wave" of artificial intelligence in oncodermatology when compared to the ISIC 2018 AI, the AI diagnoses in category 7 in the study were equivalent to those of the leading specialists. The absolute difference in accuracy compared to the decisions of the leading specialists was 1.2%, and in contrast, it exceeded those of the young specialists by 21.5%. The balanced multi-class accuracy (average completeness score) of the above 7 diagnoses was 65.9% for category 7, 52.2% for ISIC 2018, 73.8% for leading specialists, and 35.5% for young specialists [15].

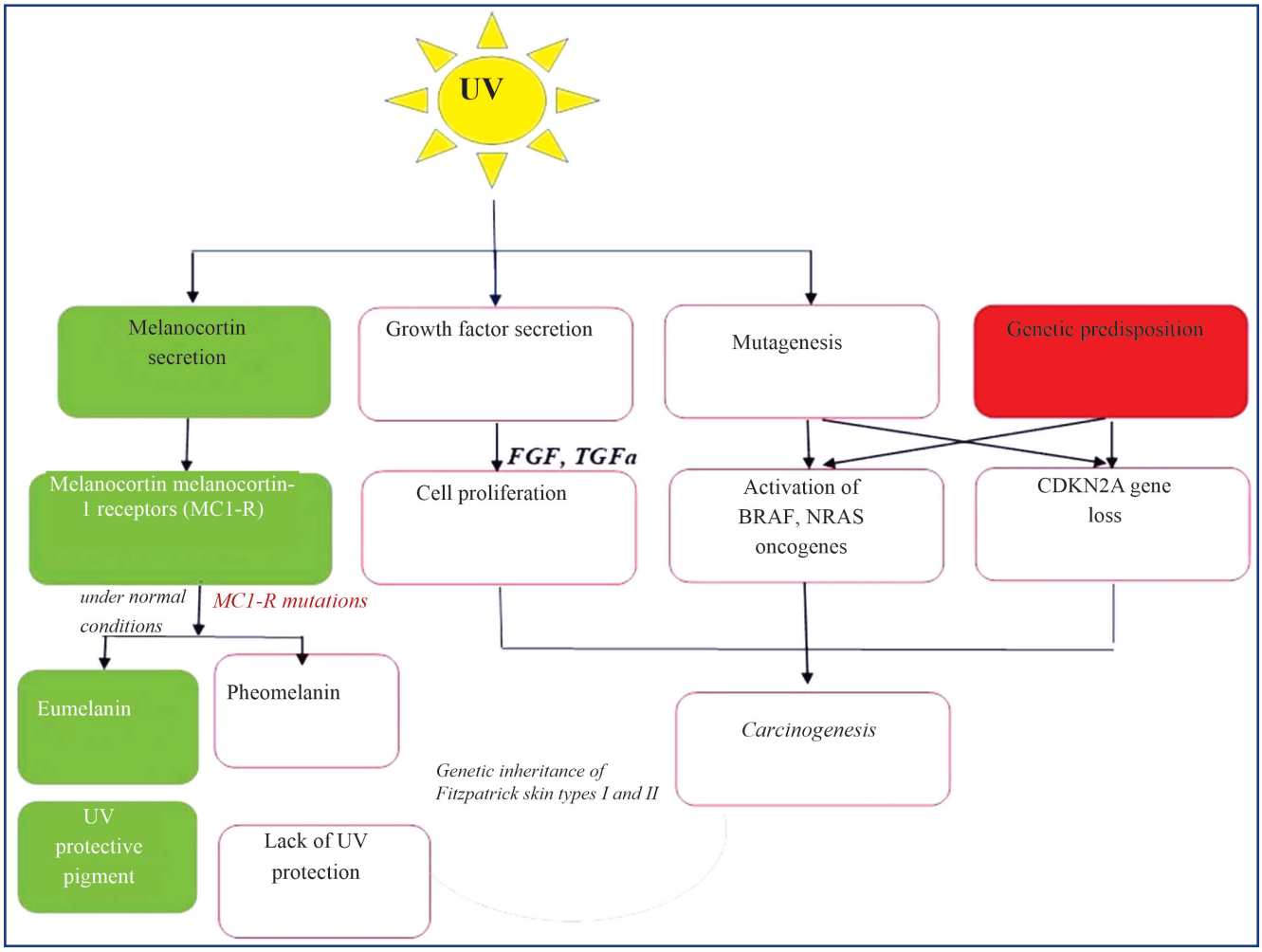

Figure 2 – Involvement of the CDKN2A gene in the pathogenesis of malignant skin melanoma

Genetic testing for the CDKN2A gene. The *CDKN2A gene*, a cyclin-dependent kinase 2a inhibitor, is located on chromosome 9. It encodes several proteins, the most studied of which are p16ink4a and p14arf, which slow cell division and act as a TSC suppressor. Normally, the CDKN2A gene is involved in the prevention of MSM, but when mutated, it increases the risk of developing MSM. Mutations in *CDKN2A*, along with multiple dysplastic nevus syndrome, cause FAMMM syndrome, i.e., familial atypical multiple myeloma inherited in first-degree relatives in the autosomal dominant type [16, 17]. Environmental factors (ultraviolet light) and genetic heredity (CDKN2A, CDK4, MC1R, BRAF, p16/ARF genes) lead to the accumulation of genetic mutations in melanocytes. As a result, oncogenes are activated, tumor suppressor genes are suppressed, and DNA repair processes are impaired [18]. This, in turn, leads to proliferation, pathologic angiogenesis, penetration of MSM into tissues, and evasion of immune re-

sponse (Figure 2). Genetic testing for MSM susceptibility genes is recommended in families with MSM after a suitable candidate has been selected and appropriate counseling has been provided to the patient. Currently, access to genetic testing depends on the geographic distribution of the disease, with 5-12% of cases being "familial" [19], and the proposed criteria for genetic evaluation are used in countries with very high incidence, such as Australia. Genetic testing of the CDKN2A gene has been available for over 20 years. However, the use of multigene panels to test for hereditary MSM is increasingly being implemented in clinical practice, increasing the ability to identify pathogenetic variants [20]. Multigene testing is particularly important if there is a family history of other cancers, as some genes predisposing to MSM may be associated with other hereditary cancers (e.g., pancreatic cancer). This facilitates a personalized approach to testing [21].

Discussion: Early detection of MSM is a challenging task that requires a multidisciplinary approach. The dermatoscopy and confocal microscopy methods presented in this article are more widely used, easier to apply, and relatively affordable than the electro-impedance spectroscopy method. Although the Nevisense electroimpedance spectroscopy method has demonstrated its superiority in detecting various types of skin neoplasms, it is not available to Onco-dermatologists and patients. The ACTRN126200000000695909 study on AI-based mobile dermatoscopic applications is the first prospective study to validate the potential of artificial intelligence-based MSM diagnostics using dermatoscopic imaging in a clinical setting for all clinically relevant classes of pigmented lesions. The importance of the study is underscored by the fact that the results were obtained using simple cell phone technology with no available hardware, unlike previous, more expensive, stand-alone devices. It is important to inform people with mutations in the "familial" MSM and CDKN2a genes about preventive measures. They should be instructed in photoprotection techniques and monthly self-examination, and for high-risk individuals, the frequency of examinations by an Oncologist or Dermatologist should be increased to once every 3-12 months.

Conclusion: Effective methods and technologies for early detection of MSM are now becoming available. However, one of the main challenges is implementing these methods in clinical practice for rational use in relation to the patient. The requirements for diagnostic methods include high diagnostic accuracy of methods, ease of use, digital registration of results and binary responses of diagnostic systems, and economic accessibility. This considers the need for training of health care providers, minimal time commitment for the patient and physician, and convenience for the patient. Unfortunately, a modern noninvasive diagnostic method that meets all these requirements has not yet been found. This situation means that the physician chooses an available method rather than an effective one for the patient. Thus, the human factor can be considered one of the obstacles to early detection of MSM.

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АНДАТПА

ҚАТЕРЛІ ТЕРІ МЕЛАНОМАСЫН ЕРТЕ САТЫДА АНЫҚТАУДЫҢ ЗАМАНАУИ ӘДІСТЕРІ: ӘДЕБИ ШОЛУ

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Өзектілігі: *Қатерлі тері меланомасы терінің қатерлі түзілістерінің ішіндегі ең қауіптісі болып табылады және дүние жүзі бойынша онкологиялық аурулар құрылымында тоғызыншы орында. Алдын алу шараларының қарапайымдылығы мен онкологиядағы визуалды түрде қолжетімді локализацияға жататынына қарамастан, терінің қатерлі меланомасымен сырқаттанушылық дүние жүзінде жыл сайын өсу үстінде. Сондықтан да, аурудың ерте сатыда анықтау мен алдын алу әдістерін жетілдіру бүгінгі таңда қоғамдық денсаулық сақтау саласындағы маңызды міндет болып табылады. Ерте сатыда анықтау әдістерінің арасында «алтын стандарт» ретінде дерматоскопия болып қала бермек және заманауи жабдықтардың барлығы да осы әдіске негізделген. Сонымен қатар, сырқаттанушылық жоғары аймақтарда «отбасылық меланоманы» анықтайтын арнайы генетикалық тестілеу әдістері де қарастырылған.*

Зерттеудің мақсаты *– тері меланомасын ерте сатыда анықтаудың заманауи әдістерінің мүмкіндіктерін сипаттау.*

Әдістері: *Scopus, PubMed арнайы ғылыми іздеу жүйелері арқылы 2014-2024 жылдар аралығындағы дереккөздерден тері меланомасын ерте сатыда анықтаудың заманауи әдістері зерттелді.*

Нәтижелері: *Мақалада сипатталған дерматоскопия мен конфокальды микроскопия әдістері қарапайымдылығы мен қолжетімділігінің арқасында, бейінді дәрігерлердің бірінші кезектегі таңдау әдісі болып қалып отыр. Невисенс жүйесі арқылы жүргізілетін электроимпедансты спектроскопия әдісінің диагностикалық құндылығы жоғары болғанымен, науқас пен дәрігерге қолжетімсіз. Ұялы телефондағы дерматоскопиялық қосымшаларға негізделген жасанды интеллект технологиясының болашағы зор, себебі екі жаққа да қолжетімді ұялы телефон негізінде жасалған. Популяциядағы сырқаттанушылық көрсеткіштері жоғары дүние жүзінің аймақтарында отбасылық тұқым қуалайтын қатерлі тері меланомасын анықтауға CDKN2A геніне генетикалық тестілеу жүргізіледі.*

Қорытынды: *Технологиялық прогрестің жалғасуымен тері меланомасын диагностикалауда заманауи әдістердің қолданылуы тиімділік, үнемділік, қарапайымдылық, қолжетімділік сияқты принциптерге негізделуі керек.*

Түйінді сөздер: *қатерлі тері меланомасы, ерте сатыда анықтау, инвазивті емес әдістер, отбасылық меланома.*

АННОТАЦИЯ

СОВРЕМЕННЫЕ МЕТОДЫ ВЫЯВЛЕНИЯ ЗЛОКАЧЕСТВЕННОЙ МЕЛАНОМЫ КОЖИ НА РАННЕЙ СТАДИИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Меланома кожи является самым опасным злокачественным новообразованием кожи и занимает девятое место в структуре онкологических заболеваний во всем мире. Несмотря на простоту профилактических мер и тот факт, что меланома кожи относится к опухолям визуально доступной локализации, заболеваемость злокачественной меланомой кожи ежегодно растет во всем мире. Поэтому совершенствование методов выявления и профилактики на ранней стадии является сегодня важнейшей задачей общественного здравоохранения. Среди методов обнаружения на*

ранних стадиях дерматоскопия остается «золотым стандартом», и все современное оборудование основано на этом методе. Кроме того, в регионах с высокой заболеваемостью также предусмотрены специальные методы генетического тестирования, которые позволяют выявить «семейную меланому».

***Цель исследования** – описание возможностей современных методов выявления меланомы кожи на ранней стадии.*

***Методы:** С помощью специальных научных поисковых систем Scopus, PubMed изучены современные методы раннего выявления меланомы кожи по источникам за период 2014-2024 гг.*

***Результаты:** Методы дерматоскопии и конфокальной микроскопии, описанные в статье, благодаря своей простоте и доступности остаются методом приоритетного выбора профильных врачей. Хотя метод электроимпедансной спектроскопии, проводимый через систему Невисенс, имеет высокую диагностическую ценность, он недоступен для пациента и врача. Технология искусственного интеллекта, основанная на дерматоскопических приложениях в мобильных телефонах, является многообещающей, поскольку она основана на мобильном телефоне, доступном для обеих сторон. В регионах с высокими показателями заболеваемости населения меланомой кожи проводится генетическое тестирование гена CDKN2A на выявление семейной наследственной злокачественной меланомы кожи.*

***Заключение:** По мере продолжения технологического прогресса применение современных методов в диагностике меланомы кожи должно основываться на таких принципах, как эффективность, экономичность, простота, доступность.*

***Ключевые слова:** злокачественная меланома кожи, выявление на ранней стадии, неинвазивные методы, семейная меланома.*

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NEW ASPECTS IN THE USE OF MULTIMODAL ANALGESIA DURING SURGICAL INTERVENTIONS IN CANCER PATIENTS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Multimodal analgesia is an important tool in postoperative pain management in cancer patients. It provides a comprehensive approach that minimizes side effects, improves recovery, and improves the patient's quality of life in the postoperative period.*

The study aimed to *generalize current data from systematic reviews, meta-analyses, and randomized controlled trials that consist of strategies and new aspects of multimodal analgesia for oncological surgery. An important aspect is the identification of effective methods for pain management in patients who have undergone surgery due to cancer.*

Methods: *The Cochrane Library, PubMed, and Embase were searched to identify randomized controlled trials, systematic reviews, and meta-analyses published in English from 2019 to 2024 that focused on the results of the use and comparison of different methods of multimodal analgesia during surgical interventions in patients with cancer.*

Results: *As a result of the analysis of data from large scientific studies and meta-analyses, the advantage of opioid-sparing methods in multimodal analgesia was established, as well as the widespread use of ultrasound-guided peripheral blocks.*

Conclusion: *A multimodal standardized method of pain relief with ropivacaine (regional blocks) in combination with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) has the best analgesic effect in patients undergoing surgery for cancer and can effectively inhibit early postoperative inflammatory reactions and promote postoperative recovery without increasing the incidence of adverse reactions and complications.*

Keywords: *multimodal analgesia, patients with cancer, ultrasound-guided regional blockades.*

Introduction: Historically, surgical pain (both intraoperative and postoperative) has been treated primarily with strong opioid regimens. Opioids are effective in reducing pain but have undesirable side effects in this patient population, the most important of which is respiratory depression. Other side effects include sedation, altered mental status, constipation, postoperative nausea, vomiting, urinary retention, and pruritus. The clinical significance of these side effects varies from person to person, but opioid side effects hinder the ultimate goal of accelerating the recovery pathway, namely, faster recovery from surgery and return to baseline functional status. Regardless of the complexity of the surgical procedures (major or minor), postoperative opioid administration can result in persistent or chronic opioid use in 5% to 15% of patients, depending on the duration of initial postoperative opioid use [1].

For this reason, enhanced recovery pathways (for any surgical specialty, including thoracic and breast surgeries) tend to use multimodal analgesic regimens that are opioid-sparing in combination with regional techniques such as interfascial blocks when possible [2-3].

The classes of drugs that can be used for perioperative analgesia in a multimodal approach are diverse and include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, NA receptor antagonists, glucocorticoids, and alpha-receptor antagonists. The 2019 Enhanced Recovery After Surgery (ERAS) Society guidelines detailed the perioperative analgesics used and the available data for several drug classes. They made a "strong" recommendation to include acetaminophen/NSAID combination, ketamine and dexamethasone, and paravertebral block as multimodal analgesia [4].

The study aimed to generalize current data from systematic reviews, meta-analyses, and randomized controlled trials that consist of strategies and new aspects of multimodal analgesia for oncological surgery. An important aspect is the identification of effective methods for pain management in patients who have undergone surgery due to cancer.

Materials and methods: The Cochrane Library, PubMed, and Embase electronic database were searched to identify randomized controlled trials, systematic reviews, and meta-analyses published in English from 2019

to 2024 that focused on the results of using and comparing different methods of multimodal analgesia during surgical interventions in patients with cancer. The exclusion criteria were RCTs and systematic reviews, meta-analyses, and scientific articles on the use of multimodal analgesia in pregnant women and children with cancer.

Results: Studies that reflect new aspects of multimodal analgesia are presented in Table 1.

Table 1 – Effectiveness of interfascial blockades in various surgical interventions in patients with oncological diseases

Authors	Year of publication	Type of Research	Cohort	Key Results
Mian BM et al. [1]	2023	Cohort study	N=686	Efficacy of non-opioid alternative methods of multimodal analgesia
Genc C. et al. [2]	2022	RCT	N=90	Equal effectiveness of blockade (fascia of the erector spinae, fascia of the pectoralis, and serratus muscles) and opioid analgesics
Edwards JT et al. [5]	2021	RCT	N=64	30% reduction in 24-hour opioid consumption following serratus interfascial block following mastectomy
Kaur U. et al. [6]	2020	RCT	N=55	Dynamic and static pain relief after blockades (muscles, erector spinae, pectoralis fascia, and serratus)
Sotome S. et al. [7]	2021	RCT	N=45	Erector spinae fascia block is equivalent to but not superior to retrolaminar block for postoperative analgesia after breast surgery.
Yao Y. et al. [8]	2019	RCT	N=68	Serratus fascia block improved the quality of recovery and postoperative analgesia in breast cancer.
Kitagawa H. et al. [9]	2024	RCT	N=64	Multimodal analgesia combined with transversus abdominis fascia block may be comparable to epidural analgesia after laparoscopic colon cancer surgery.
Kuniyoshi H. et al. [10]	2019	RCT	N=100	A case-based rectus block may be a substitute when a continuous epidural block is contraindicated as a component of postoperative multimodal analgesia.
Ma Y. et al. [11]	2024	RCT	N=72	Multimodal opioid-sparing anesthesia may be a safer and more effective alternative to anesthesia in elderly patients, minimizing opioid-related side effects.
Yeo J. et al. [12]	2022	RCT	N=97	Multimodal analgesia (pregabalin + transversus abdominis fascia block + tramadol) successfully controlled postoperative pain and was non-inferior to morphine-based patient-controlled analgesia.
Toleska M. et al. [13]	2023	RCT	N=60	Patients in the opioid-sparing group had the lowest pain scores in the first 72 hours after open colorectal surgery.
Huang D. et al. [14]	2020	RCT	N=77	Bilateral posteromedial quadratus dorsi fascia block reduces morphine consumption in the setting of multimodal analgesia compared with lateral transversus abdominis fascia block after laparoscopic colorectal surgery.
Liang M. et al. [15]	2021	RCT	N=78	Postoperative ultrasound-guided posterior transversalis fascia block with rectus abdominis fascia block reduced postoperative opioid use in patients after laparoscopic radical resection of rectal cancer.
Shi R. et al. [16]	2024	RCT	N=67	Preoperative bilateral quadratus dorsi fascia block reduces postoperative morphine use.
Cao L. et al. [17]	2024	RCT	N= 84	Multimodal standardized analgesia with ropivacaine in combination with parecoxib sodium and a patient-controlled analgesia pump had a better analgesic effect.
Li X. et al. [19]	2021	RCT	N=96	In patients undergoing laparoscopic renal surgery, a preoperative single quadratus dorsi fascia block did not reduce opioid consumption but improved analgesia for up to 24 hours postoperatively.
Zhang Q. et al. [20]	2023	RCT	N=80	Non-opioid anesthesia based on thoracic paravertebral block improved the quality of early postoperative recovery in patients undergoing breast cancer surgery.
Chenesseau J. et al. [21]	2023	RCT	N=196	Surgeon-delivered paravertebral block during thoracoscopy was non-inferior to anesthesiologist-delivered paravertebral block using ultrasound in terms of opioid consumption during the first 48 hours.
De Cassai A. et al. [31]	2021	Meta-analysis	N=4074	All regional block techniques (serratus fascia, pectoralis fascia, and serratus fascia) were associated with superior analgesia and lower opioid consumption than controls.
Ahlberg H. et al. [32]	2023	RCT	N=185	Combined pectoralis fascia and serratus block before breast cancer surgery reduces postoperative morphine requirements.

A review of included meta-analyses, systematic reviews, and RCTs showed that, with advances in technology, including ultrasound (US), regional blocks had become an integral part of multimodal analgesia in oncologic surgery, and are associated with less pain, less postoperative nausea and vomiting, and shorter hospital stays in patients undergoing thoracic, urologic, and breast surgery [5-7].

An RCT by Yao et al. examined the use of ultrasound-guided serratus plane block (SPB) for pain relief after breast cancer surgery. According to the 40-item Quality of Recovery questionnaire, the global median score at 24 hours after surgery was significantly higher in the SPB group (158 [153.8-159.3]) than in the placebo (saline) control group (141 [139-145.3]), with a mean difference of 15 (95% CI: 13 to 17, p<0.001) (Table 2) [8].

Compared with the control group, postoperative pain scores (assessed by visual analog scale) at rest were significantly lower at 24 hours in the SPB group (P<0.001) (Figure 1).

Preoperative SPB reduced postoperative total opioid consumption, incidence of postoperative nausea and vomiting, and time to discharge from the anesthesia

care unit. In addition, patient satisfaction scores were higher in the SPB group.

Although continuous epidural analgesia remains the standard method and part of multimodal perioperative analgesia, recent advances in ultrasound devices allow good visualization of block needles, thereby facilitating the placement of catheters in appropriate positions for continuous peripheral nerve blocks in the perioperative period. In cases where epidural analgesia is contraindicated, continuous plane blocks can be considered as an alternative to epidural analgesia for adequate pain management [9].

Table 2 – 40-item Postoperative Quality of Recovery Questionnaire, 24-hour global assessment [8]

Variables	Serratus muscle block, n=34	Control group, n=34	Median difference (95% CI)	Probability value
Global Quality of Recovery Questionnaire – 40 items	158[153.8 to 159.3]	141[139 to 145.3]	15[13 to 17]	<0.001
Emotional status	31[28.8 to 33]	28[27 to 29]	3[2 to 4]	<0.001
Physical comfort	50[49 to 51]	43.5[42 to 46]	6[5 to 8]	<0.001
Physical independence	14[12.8 to 16]	13[12 to 15]	1[0 to 2]	0.168
Psychological support	28[29 to 30]	28[26 to 29]	1[0 to 2]	0.061
Pain	33[32 to 34]	28[27 to 30]	4[4 to 5]	<0.001

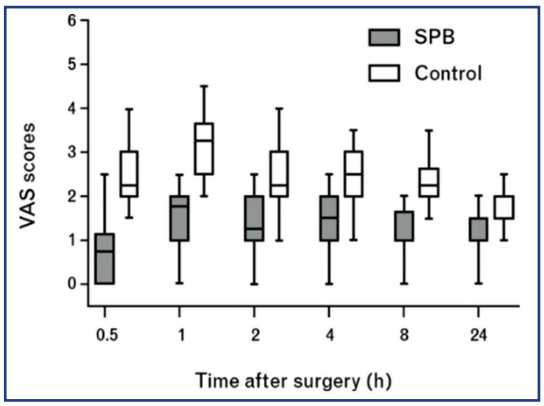


Figure 1 – Box plot of postoperative visual analog scale at rest in patients receiving serratus muscle block (SPB) with 0.5% ropivacaine compared to saline [8]

In an RCT comparing the results of continuous epidural analgesia (CEA) and continuous rectus sheath block (CRSB) conducted by H. Kuniyoshi et al., the postoperative mean pain score in the CEA and CRSB groups during movement and rest was less than three during the observation period (Figure 2) [10].

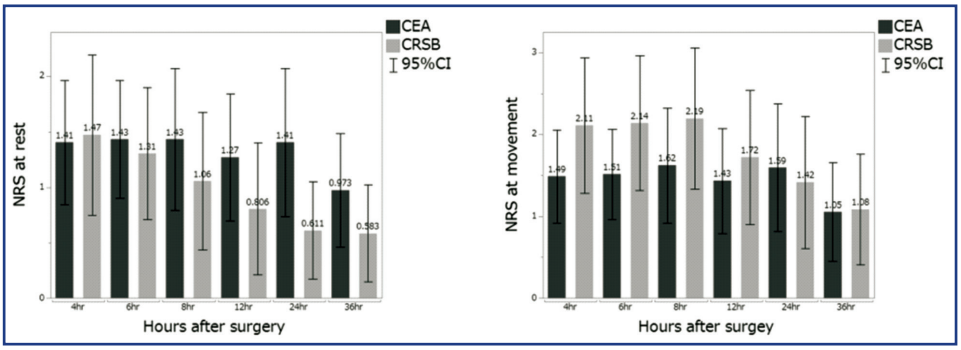


Figure 2 – Postoperative Numeric Rating Scale in the Continuous Epidural Analgesia (CEA) Group and the Continuous Rectus Spinal Block (CRSB) Group at Movement and Rest. Data are presented as mean and 95% CI [10]

There was no significant difference between the groups in the need for intravenous patient-controlled analgesia (IV-PCA), the total number of IV-PCA requests, and the frequency of rescue medications. Rescue analgesics included NSAIDs, acetaminophen, and buprenorphine. Table 3 shows no significant difference between the CEA and CRSB groups concerning rescue medications [10].

Planar regional blocks performed under ultrasound control have become widespread in combination with perioperative multimodal analgesia in other areas of

oncological surgery, including urological and abdominal operations [11-13].

According to the ERAS guidelines, various analgesic methods are recommended for minimally invasive colorectal surgery, such as intravenous patient-controlled analgesia (IV-PCA) in combination with acetaminophen, NSAIDs, or opioid agonists, as well as incisional wound infiltration with local anesthetics, transverse abdominis plane block, ultrasound-guided rectus abdominis compartment block, or other analgesic methods [14–17].

Table 3 – Duration, overall frequency, frequency of success, frequency of failure of rescue drugs [10]*

	Extended epidural analgesia	Extended rectus abdominis block	Meaning probabilities
Duration of intravenous patient-controlled analgesia (min)	2040 (1560-2460)	2310 (1515-2760)	0.50
The overall frequency of use of intravenous patient-controlled analgesia	30 (8.5. 49.5)	22 (4-68)	0.83
The success rate of intravenous patient-controlled analgesia	14 (7.5-24)	11.5 (4-24.75)	0.53
Incidence of failure of intravenous patient-controlled analgesia	13 (1.5 32.5)	8.5 (1-42.75)	0.97
Frequency of use of rescue medications (NSAIDs, acetaminophen, and buprenorphine)	2 (0-4.5)	1 (0-3.75)	0.54

*Note: *Data are presented as median (quartile range)*

Despite the advent of laparoscopic and robotic surgery, open colectomy continues to be performed worldwide. Such procedures are associated with significant postoperative pain. In 2016, the PROSPECT task force proposed recommendations based on a systematic review of 93 randomized controlled trials (RCTs) on pain relief after open colectomy. Following registration on PROSPERO (CRD4202338800), a systematic review of the literature on analgesia after open colectomy was conducted according to the PROSPECT methodology. Embase, MEDLINE, and Cochrane databases were searched specifically for this study for RCTs published between 1 January 2016 and 1 January 2022. The analgesic regimen for open colectomy should include intraoperative paracetamol and specific COX-2 inhibitors or NSAIDs (colon surgery only), epidural anesthesia, and continued analgesia in the postoperative period using opioids as rescue analgesics. If epidural anesthesia is not possible, bilateral TAP block or intravenous lidocaine is recommended. Safety issues should be emphasized: local anesthetics should not be administered via two different routes simultaneously. Careful dosing and monitoring are necessary due to the risk of toxi-city [18].

An RCT by Li et al. shows that quadratus lumborum block (QLB) is one of the modern methods of regional anesthesia that is used to control pain, both somatic and visceral, in the abdominal area, including the lateral and anterior parts, during urological surgeries.

Compared with the control group, postoperative somatic pain scores at both rest and cough were significantly lower in the group of patients who received QLB block via the lateral approach (at rest, median difference -1, P<0.001; during cough, median difference -2 to -1, P<0.001) and in patients who received QLB block via the posterior approach (at rest, median difference -1, P<0.001; during cough, median difference -2 to -1, P<0.001) (Figure 3) [19].

The use of opioids in the perioperative period is associated with increased postoperative nausea and vomiting, hyperalgesia and chronic pain after surgery, and a variety of other adverse events, particularly relevant in the recovery of patients who have undergone breast cancer surgery. In an RCT by Zhang et al., the quality of recovery of patients after breast cancer surgery according to the QoR-15 (15-item Quality of Recovery) scale was 100% among 40 patients who underwent multimodal analgesia without opioids (NSAIDs + ultrasound-guided paravertebral block), and 82.5% among 40 patients in the control group (P=0.012) (Figure 4) [20].

However, even if US-guided paravertebral block is a reliable method, failure of pain control is a common problem due to technical problems and insufficient personnel training, and therefore, the procedure fails in 6-10% of cases. Thus, paravertebral block with video-assisted thoracoscopy-VATS in patients undergoing lung tumor surgery may be an option with the advantages of thoracoscopic direct visualization of the pleural cavity, ensuring correct intercostal space definition and insertion depth, especially in overweight patients with poor echogenicity of US images. Pain scores on the visual analog scale at rest and with cough at 4, 6, 12, and 48 hours after PVB were similar in the two groups (Figure 5) [21].

A systematic review by BC Go et al. comparing multimodal analgesia with a control group (a total of 10 studies involving 1253 patients (multimodal analgesia group, n=594; control group, n=659)) found that gabapentinoids were the most commonly used drugs (72.9%), followed by NSAIDs (44.6%), acetaminophen (44.3%), corticosteroids (25.1%), ketamine (7.2%), and nerve blocks (3.4%). Eight studies reported a significant reduction in postoperative opioid use in the multimodal analgesia groups [23]. A meta-analysis by CC Chang et al. found a 46% reduction in the incidence of chronic postoperative pain compared with acute pain after breast cancer surgery (95% CI: 0.25-0.85) [24]. Also, the combination of perioperative oral pregabalin and postoperative S-ketamine effectively prevented chronic pain after breast cancer surgery and reduced acute postoperative pain. It decreased postoperative opioid consumption, although, according to the authors, the data obtained were not analyzed in sufficient detail and require larger-scale studies [25-27].

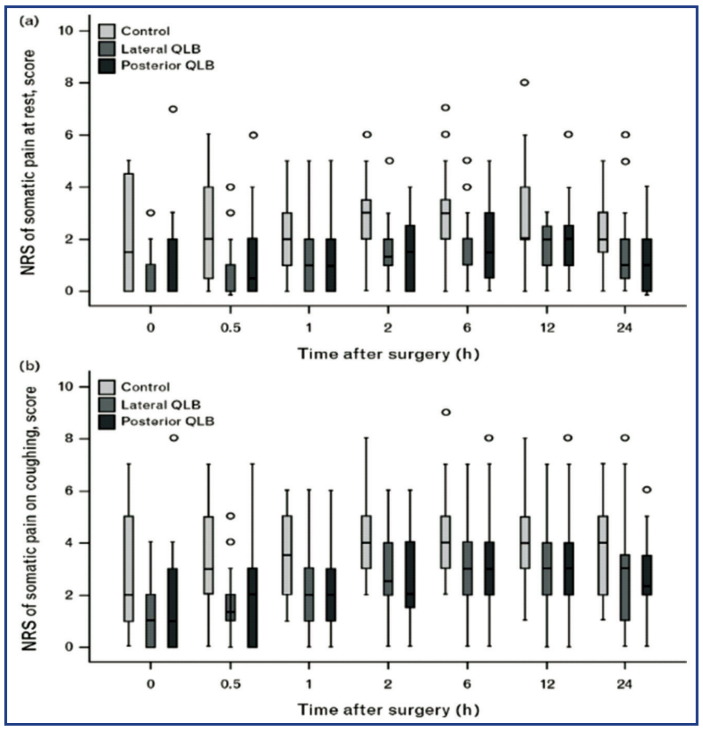


Figure 3 – Numerical rating scale for assessing somatic pain and visceral pain during the first 24 hours after surgery [19]

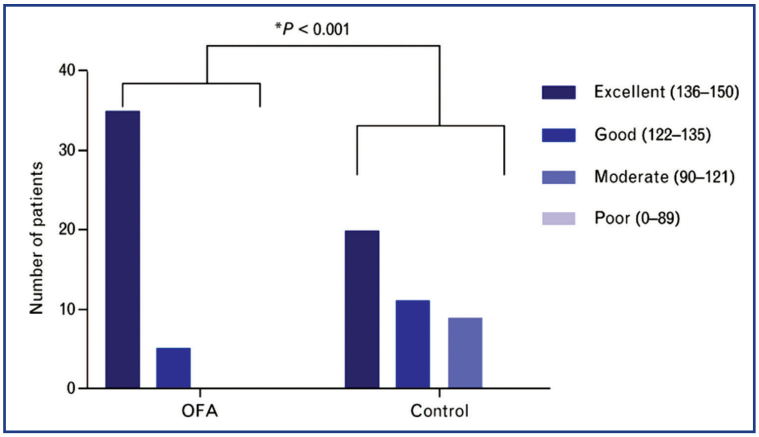
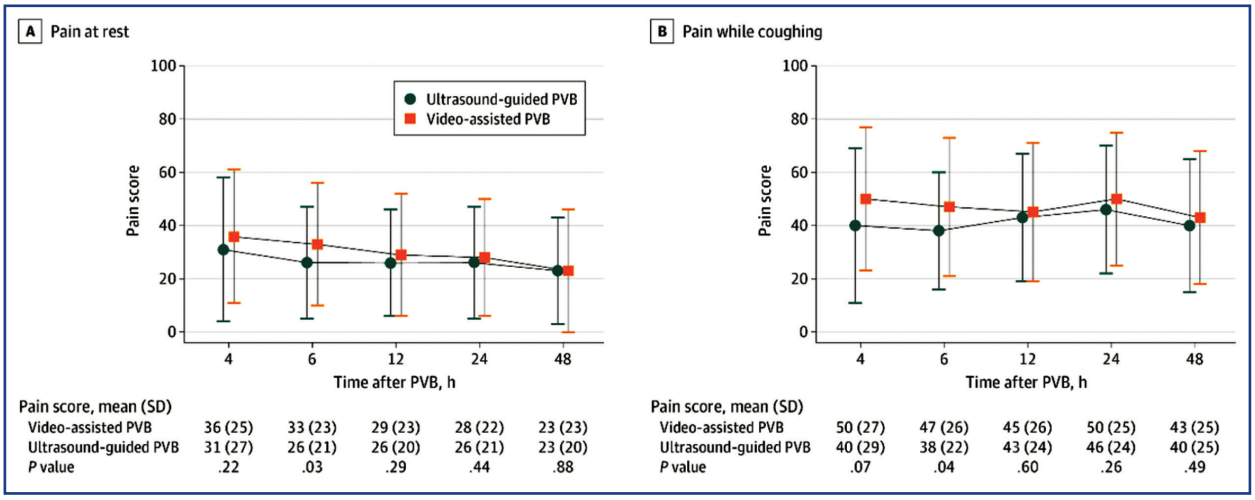


Figure 4 – Distribution of patients by categories of quality of recovery after surgery [20]



Pain score, mean (SD)					
Video-assisted PVB	36 (25)	33 (23)	29 (23)	28 (22)	23 (23)
Ultrasound-guided PVB	31 (27)	26 (21)	26 (20)	26 (21)	23 (20)
P value	.22	.03	.29	.44	.88

Pain score, mean (SD)					
Video-assisted PVB	50 (27)	47 (26)	45 (26)	50 (25)	43 (25)
Ultrasound-guided PVB	40 (29)	38 (22)	43 (24)	46 (24)	40 (25)
P value	.07	.04	.60	.26	.49

Figure 5 – Postoperative pain according to a visual analog scale at rest (A) and with cough (B) at 4, 6, 12, 24, and 48 hours after video-assisted paravertebral block (VAPV) compared with ultrasound-guided VAPV [21]

Treatment of postoperative pain after head and neck cancer surgery is also a complex issue, along with other oncological diseases, requiring a careful balance between the analgesic properties and side effects of analgesic drugs [22].

In recent years, intravenous lidocaine has become part of opioid-sparing multimodal analgesia protocols, and Wallon et al. conducted an RCT to assess morphine requirements during the first 48 postoperative hours after intraoperative lidocaine infusion during major head and neck cancer surgery involving 118 patients (lidocaine n = 57; placebo n = 61). No significant difference in morphine consumption during the first 48 hours after surgery was observed in the lidocaine group compared with the placebo group [28].

Discussion: Multimodal analgesia is a combination of different pain relief methods that affect different mechanisms of the pain process. In oncosurgery, multimodal analgesia is used to minimize pain syndrome and reduce the need for opioids, which can cause several undesirable side effects, such as addiction, respiratory depression, and nausea.

Interfascial blocks (e.g., intercostal block of the fascia between the pectoralis major and minor muscles) are an important component of multimodal analgesia, allowing effective pain control, especially in the chest area after chest surgery [29].

In Russian and foreign literature, various techniques of interfascial blockades are described, such as paravertebral blockades for patients with oncological diseases of the chest, which have been proven to be highly effective in reducing postoperative pain syndrome and improving the general condition of patients.

A.Yu. Morunova et al. compared the effectiveness of interfascial erector spine plane (ESP)-block and CEA since these methods not only effectively control pain but also reduce the intensity of surgical stress, which can affect the levels of stress markers, such as cortisol and interleukin-6 (IL-6). The study revealed that the cortisol level in patients receiving ESP-block and CEA was within the normal range during surgery. A day later, the cortisol level statistically significantly decreased in ESP-block patients. On the 3rd day after surgery, a moderate increase in cortisol levels was noted in patients of both groups. In patients of the control group, who underwent general anesthesia without regional pain relief techniques, the IL-6 level during surgery was highest (p=0.012). A day after surgery, the highest IL-6 levels were observed in patients in the ESP-block group. The need for opioid analgesics was statistically significantly higher in patients in the control group (p=0.004). Adverse events in the form of urinary retention were recorded in 2 (6%) patients in the CEA group [30].

Conclusion: Interfascial blockades have proven to be an important component of anesthetic management, especially in minimizing postoperative pain and accelerating recovery. In particular, in the context of laparoscopic surgeries, where the impact on tissues is minimal, but patients may experience significant pain after the intervention, interfascial regional blockades can significantly reduce the need for opioid analgesics, which reduces the risk of side effects and complications [31-32].

The introduction of these blocks into multimodal analgesia, especially in the context of the ERAS protocol, aims to improve the postoperative recovery of patients, which is especially important for cancer patients who may experience more severe postoperative morbidity.

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АҢДАТПА

ОНКОЛОГИЯЛЫҚ НАУҚАСТАРҒА ХИРУРГИЯЛЫҚ ОТА ЖАСАУ КЕЗІНДЕ МУЛЬТИМОДАЛДЫ АНАЛЬГЕЗИЯНЫ ҚОЛДАНУДЫҢ ЖАҢА АСПЕКТІЛЕРІ: ӘДЕБИЕТТЕРГЕ ШОЛУ

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Өзектілігі: *Мультимодальды анальгезия онкологиялық науқастарда операциядан кейінгі ауырсынуды басқарудың маңызды құралы болып табылады. Ол жанама әсерлерді азайтатын, қалпына келтіруді жақсартатын және операциядан кейінгі кезеңде пациенттің өмір сүру сапасын жақсартатын кешенді тәсілді ұсынады.*

Зерттеудің мақсаты: *Онкологиялық хирургия үшін мультимодальды анальгезиядағы стратегиялар мен жаңа аспектілерді қарастыратын жүйелі шолулардан, мета-талдаулардан және рандомизацияланған бақыланатын сынақтардан ағымдағы дәлелдемелерді біріктіру. Маңызды аспект – қатерлі ісікке байланысты операция жасалған науқастарда ауырсынуды емдеудің тиімді әдістерін анықтау.*

Әдістері: *Қатерлі ісікке шалдыққан науқастарға хирургиялық ота жасау кезінде мультимодальды анальгезияның әртүрлі әдістерін қолдану және салыстыру нәтижелеріне бағытталған рандомизацияланған бақыланатын сынақтар Cochrane Library, PubMed, Embase электронды базасында 2019-2024 жылдар аралығында ағылшын тілінде жарияланған жүйелі шолулар мен мета-талдауларды анықтау үшін іздестірілді.*

Нәтижелері: *Ірі ғылыми зерттеулер мен мета-анализдердің деректерін талдау нәтижесінде мультимодальды анальгезияда опиоидты сақтау әдістерінің артықшылығы, сондай-ақ ультрадыбыстық басқарылатын перифериялық блокадаларды кеңінен қолданылуы анықталды.*

Қорытынды: *Ацетаминофенмен және стероид емес қабынуға қарсы препараттармен (ҚҚСП) біріктірілген ропивакаинмен (аймақтық блокадалар) ауыруды басудың мультимодальды стандартталған әдісі қатерлі ісікке хирургиялық операция жасалған науқастарда анальгетикалық әсерге ие және операциядан кейінгі ерте қабыну реакцияларын тиімді тежей алады және жағымсыз реакциялар мен асқынулардың жиілігін арттырмай, операциядан кейінгі қалпына келтіруге ықпал ете алады.*

Түйінді сөздер: *мультимодальды анальгезия, қатерлі ісікпен ауыратын науқастар, ультрадыбыстық бақылаумен жасалынатын аймақтық блокадалар.*

АННОТАЦИЯ

НОВЫЕ АСПЕКТЫ ПРИМЕНЕНИЯ МУЛЬТИМОДАЛЬНОЙ АНАЛЬГЕЗИИ ПРИ ОПЕРАТИВНЫХ ВМЕШАТЕЛЬСТВАХ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Мультимодальная анальгезия является важным инструментом в послеоперационном управлении болью у онкологических пациентов. Она обеспечивает комплексный подход, который минимизирует побочные эффекты, улучшает восстановление и повышает качество жизни пациента в послеоперационном периоде.*

Цель исследования *– обобщение актуальных данных из систематических обзоров, мета-анализов и рандомизированных контролируемых исследований, которые касаются стратегии и новых аспектов в мультимодальной анальгезии при онкологических оперативных вмешательствах. Важным аспектом данной работы является выявление эффективных методов управления болевым синдромом у пациентов, перенесших операцию на фоне онкологического заболевания.*

Методы: *Был проведен поиск в электронных базах данных Cochrane Library, PubMed, Embase для выявления рандомизированных контролируемых исследований, систематических обзоров и мета-анализов, опубликованных на английском*

языке с 2019 по 2024 годы, в которых основное внимание уделялось результатам применения и сравнения различных методов мультимодальной анальгезии при оперативных вмешательствах у пациентов с онкологическими заболеваниями.

Результаты: *В результате анализа данных крупных научных исследований и мета-анализов было установлено преимущество опиоид-сберегающих методов в рамках мультимодальной анальгезии, а также широкое распространение применения периферических блокад, проводимых под ультразвуковым контролем.*

Заключение: *Мультимодальный стандартизированный метод обезболивания ропивакаином (регионарные блокады) в сочетании с ацетоаминофеном и нестероидными противовоспалительными препаратами (НПВП) оказывает лучший анальгезирующий эффект на пациентов, перенесших оперативные вмешательства по поводу онкологических заболеваний и может эффективно ингибировать ранние послеоперационные воспалительные реакции и способствовать послеоперационному восстановлению без увеличения частоты побочных реакций и осложнений.*

Ключевые слова: *мультимодальная анальгезия, пациенты с онкологическими заболеваниями, регионарные блокады под УЗ-контролем.*

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QUALITY CONTROL IN MOLECULAR GENETICS LABORATORY: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Integrating molecular biomarkers with rigorous quality control (QC) measures in laboratory settings is essential for enhancing early detection strategies and prognostic evaluation in cancer patients. Precision and QC in laboratory diagnostics of oncological diseases have become particularly significant in the widespread implementation of targeted and personalized therapy.*

The study aimed to *review publications evaluating quality control in biomarker identification within molecular genetics laboratories, using ovarian cancer diagnostics as a case study.*

Methods: *This systematic literature review conducted in the framework of this study revealed 220 records, leading to 165 unique publications, of which 24 full-text articles were included in this review. The study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) guidelines.*

Results: *All analyzed sources showed that Implementing QC, including calibration, internal controls, and proficiency testing provided by the College of American Pathologists (CAP), significantly reduces errors despite ongoing funding constraints. The European Molecular Quality Network (EMQN) and CAP jointly offer proficiency testing programs to evaluate laboratory performance globally, ensuring consistency and reliability in testing outcomes.*

Conclusion: *Ensuring the accuracy and reliability of molecular diagnostic tests is critical in clinical settings, particularly for conditions such as ovarian cancer, where precise genetic analysis informs both diagnosis and treatment. Further advancements in early detection and personalized treatment can be achieved by integrating emerging technological innovations within robust QC framework, ultimately improving patient outcomes. Consequently, the establishment of standardized guidelines and standard operating procedures for molecular genetic testing, with a specific focus on the molecular genetic diagnosis of ovarian cancer, is imperative.*

Keywords: *molecular genetic testing, quality control (QC), BRCA1, BRCA2, polymerase chain reaction (PCR), next-generation sequencing (NGS).*

Introduction: Modern medical personalization trends require the implementation and application of advanced diagnostic technologies. In recent years, this process has experienced significant advancements, notably in oncology. Various biomarkers play a pivotal role in personalization. Accurate detection of biomarkers and genetic alterations, in particular, using advanced and precise techniques of polymerase chain reaction (PCR) and next-generation sequencing (NGS), relies on stringent QC standards, which molecular genetics laboratories must uphold to ensure diagnostic reliability [1, 2]. We utilized the diagnosis of biological and molecular markers in ovarian cancer as a case study, considering the unique characteristics of disease diagnosis and progression, the application of detection methods, and the critical role of molecular markers in therapeutic decision-making.

The study aimed to review publications evaluating quality control in biomarker identification within molecular genetics laboratories, using ovarian cancer diagnostics as a case study.

Materials and Methods: A systematic review of literature conducted in the framework of this study revealed 220 records, leading to 165 unique publications, after which 70 full-text papers were analyzed. The study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) guidelines [3] to assess worldwide QC procedures in molecular genetics laboratories that test for ovarian cancer. The research contained 25 unrelated ovarian cancer studies, excluded 15 works without QC information, 12 studies with imprecise methods, and five articles predating 2015. Eight studies passing the Critical Appraisal Skills Programme (CASP) checker with scores exceeding 80% were assembled for synthesis [4].

Search strategy: Literature sources from the PubMed, Scopus, Web of Science, and Google Scholar databases published between 2015 and 2025 were reviewed and analyzed. The research used the combination of "Quality Control" OR "Quality Assurance" together with "molecular genetics" OR "molecular diagnostics" supported by "ovarian cancer" AND "laboratory practices." A manual citation search was also performed, and references were organized using EndNote X9 to complete the research process. [5].

Exclusion criteria: Studies that failed to show laboratory or methodological details or were published before 2015 or in languages other than English were excluded.

Study selection process: The review proceeds through a clear workflow, which makes its findings strong and connected to the diagnostic QC of ovarian cancer, as shown in Figure 1.

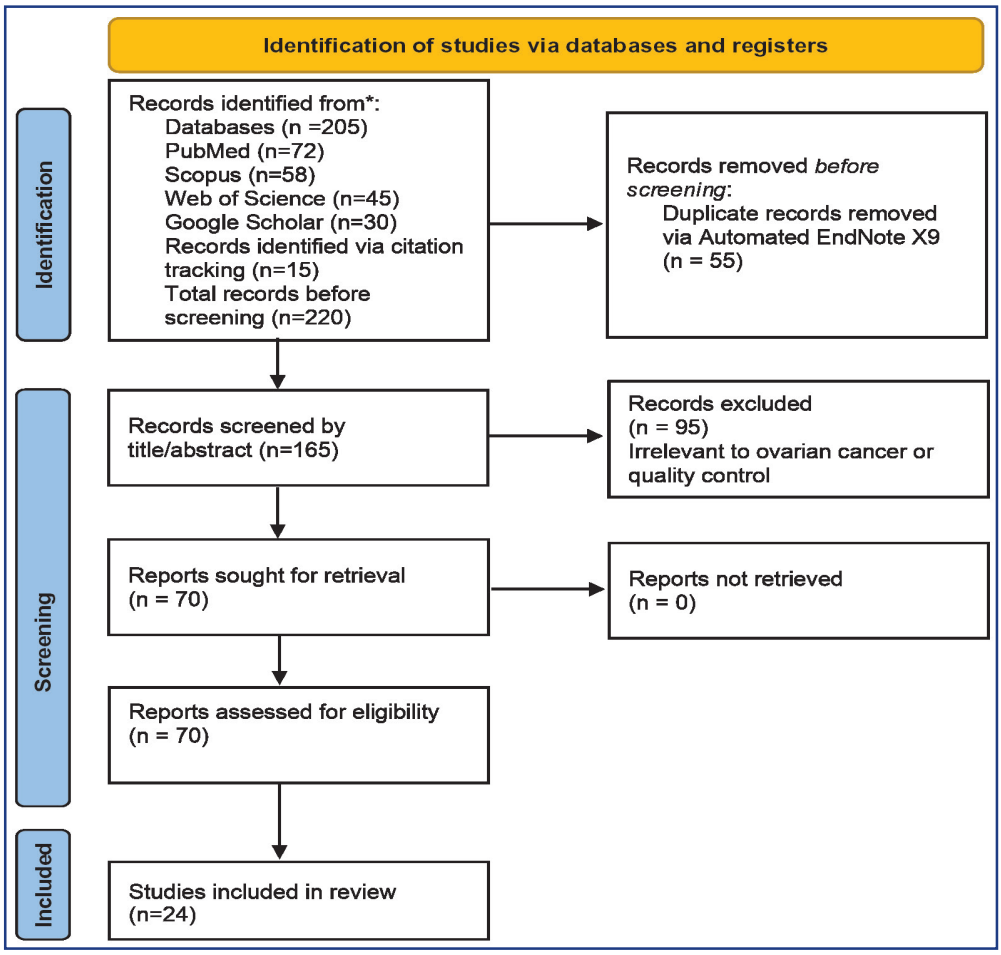

Figure 1 – PRISMA flow diagram

Results:

Quality control protocols in molecular genetics laboratories: With the rapid expansion of molecular genetic diagnostic methods in recent years, alongside the increasing number of tests and panels, the implementation and integration of rigorous QC systems in laboratories have become essential to ensure accuracy, reliability, and standardization. Since implementing genetic testing, the interest in and necessity for QC protocols to enhance testing accuracy have grown significantly. Figure 2 presents the evolution of QC protocols in molecular genetics laboratories, outlining key milestones in their development.

As shown in Figure 2, the Clinical Laboratory Improvement Amendments (CLIA) of 1988 established foundational standards, while the National Institutes of Health (NIH) and the Department of Energy (DOE) in 1997 emphasized the importance of Quality Assurance [6]. In 2009, the Centers for Disease Control and Prevention (CDC) outlined best practices for laboratory quality management [7]. The Minimum Information for Publication of Quantitative Real-Time Polymerase Chain Reaction Experiments (MIQE) guidelines, introduced in 2010, standardized quantitative PCR methodologies, followed by a QC framework in 2012 [8, 9]. The 2020 MIQE updates further refined QC measures addressing digital PCR advancements [10].

QC measures in molecular genetics laboratories are pivotal in maintaining assay integrity, minimizing diagnostic errors, and ensuring reproducibility across different testing facilities.

External quality assessment (EQA) by organizations such as the European Molecular Genetics Quality Network (EMQN) and the College of American Pathologists (CAP) is used to evaluate laboratory performance on a global level [11, 12]. These programs provide standardized proficiency testing schemes that assess laboratory practices, monitor test consistency, and identify improvement areas. By benchmarking results against international standards, EQA programs contribute to the harmonization of molecular diagnostics and reinforce best practices in genetic testing. External quality assessments from CAP and EMQN strive to improve worldwide measurement standards by accrediting laboratories through proficiency testing programs that protect pathology and laboratory medicine quality. Programs and their brief description are shown in Table 1.

QC programs in laboratories typically comprise three distinct phases. The accuracy of molecular diagnostic equipment is contingent on stringent calibration protocols.

Laboratories in the United States and Europe adhere to International Organization for Standardization (ISO) guidelines, such as ISO 15189, to maintain thermal precision in PCR machines. These calibration standards are essential for ensuring consistent amplification conditions, thereby reducing variability in test results and enhancing diagnostic accuracy [13].

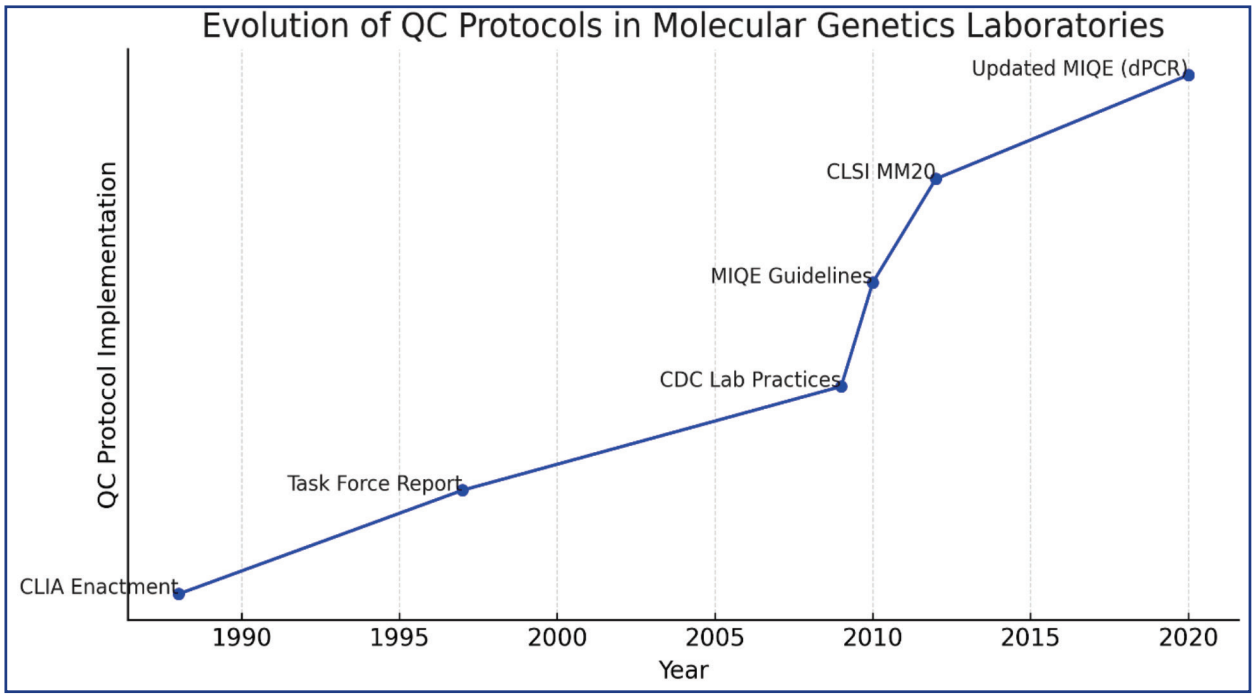

Figure 2 – Evolution of QC protocols used in Molecular Genetics Laboratories

Table 1 – External quality control programs and guidelines

Program	Description	Source
College of American Pathologists	Provides accreditation and proficiency testing for pathology and laboratory medicine.	CAP
European Molecular Genetics Quality Network	Offers external quality assessment for molecular genetics laboratories.	EMQN

Reliable molecular testing depends on rigorous assay validation and contamination detection protocols. Laboratories worldwide implement positive and negative control sample testing to assess assay performance and detect potential contaminants. Well-characterized reference samples ensure that molecular assays produce consistent and reproducible results, further strengthening diagnostic reliability [2]. QC phases are provided in Table 2.

Table 2 – Quality control protocols in molecular genetics laboratories

Quality control protocol	Description	Global examples
Calibration	Regular calibration of equipment to maintain accuracy.	Laboratories in the USA and Europe follow ISO standards for calibration.
Internal Controls	Use of positive and negative controls in each assay to validate results.	Widely implemented in accredited molecular genetics labs globally.
Proficiency Testing	Participation in external quality assessment schemes to benchmark performance.	Programs like EMQN and CAP offer proficiency testing worldwide.

Key findings from studies on quality control in molecular genetics laboratories for ovarian cancer diagnostics. With the advancement of novel diagnostic methodologies for ovarian cancer, the standards and requirements for quality control programs have undergone significant evolution. The analyzed studies underscore significant advancements in genetic testing and QC systems, particularly molecular genetic diagnostics of ovarian cancer, regardless of techniques and methods used. In 2015, Strom et al. reported that NGS achieved 99% accuracy in detecting *BRCA*1 and *BRCA*2 using strict control systems and calibration methods [14]. Other study using multigene panel testing, showed that this panel matched 95% of all results obtained through Sanger sequencing but highlights the necessity for standardization practices [15]. According to C.R. Marshall et al., Whole Genome Sequencing provided 98% sensitivity, improving by regularly implementing QC procedures [16]. D. Grafodatskaya et al. stated that testing accuracy for *BRCA1* and *BRCA2* improved when EQA was adopted along with a Limit of Detection that exceeded 10% [17]. In 2023, E.T. Kim et al. verified the use of NGS to analyze *BRCA1* and *BRCA2* genes in formalin-fixed paraffin-embedded samples by reaching 99% accuracy rates at sequencing depths exceeding 40x, eliminating unnecessary false positive test results [18]. The data from the Menon & Brash study (2023) showed that extended sequencing depth above 1000x and additional strict QC serve to reduce errors during rare variant detection [19]. And more recent study, published in 2024 by T. McDevitt et al. demonstrated reliable genetic testing through paired analysis by following EMQN guidelines and ISO 15189 standards to achieve maximum analytical sensitivity [20]. Key findings are documented in Table 3.

Table 3 – Key findings from studies on quality control (QC) in molecular genetics laboratories for ovarian cancer diagnostics

Authors	Key findings
Lincoln et al., 2015	Hereditary ovarian cancer testing through multigene panels detects more conditions yet needs strong QC procedures to achieve 95% accuracy compared to Sanger testing methods.
Strom et al., 2015	The NGS assay for BRCA1/2 reached 99% accuracy during validation through proper control implementation and calibration procedures that enhanced laboratory reliability to identify rare variants.
Marshall et al., 2020	The validation of Whole Genome Sequencing technology requires specific performance metrics to reach a sensitivity level of 98% when combined with standard QC procedures for complete ovarian cancer genetic analysis.
Grafodatskaya et al., 2021	EQA should be applied along with a Low Limit of Detection ≥10% to improve the accuracy of BRCA1/2 testing for ovarian cancer.
Kim et al., 2023	The precision of NGS validation for BRCA in ovarian FFPE reaches 99% accuracy when the QC depth exceeds 40x.
Menon & Brash, 2023	The evaluation of NGS QC focuses on mutation detection at frequencies under 1000x depth and utilizes controls to prevent errors in ovarian cancer variant identification.
McDevitt et al., 2024	Applying EMQN guidelines requires implementing ISO 15189 standards, EQA participation, and paired testing for ovarian cancer, ensuring high analytical sensitivity.

Discussion: Despite significant progress in establishing QC systems worldwide and accuracy levels of *BRCA* ½ mutations with 99% detection achieved through NGS mirror global findings, some laboratories face technical difficulties that differ from the international research focus and align with resource constraints discussion [18-19, 21, 22]. The combined initiative of standardization practice using CAP and EMQN frameworks establishes a comprehensive system beyond the diverse perspectives described by different authors [15, 21]. The work by Wang X in 2024 and Hamidi et al. (2023), along with other emerging technologies, puts this study ahead of domestic biomarker research while demonstrating the significance of QC for precision medicine advancement [23, 24].

Conclusion: In recent years, molecular genetic research has been increasingly incorporated into the routine practice of oncology institutions in the Republic of Kazakhstan, as well as into diagnostic and treatment protocols for oncological diseases, particularly ovarian cancer. Ensuring the accuracy and reliability of molecular diagnostic tests is critical in clinical settings, particularly for conditions such as ovarian cancer, where precise genetic analysis informs both diagnosis and treatment. Standardized protocols, combined with calibration, internal controls, and proficiency testing, enhance diagnostic accuracy, as demonstrated by global research studies. The continuity of laboratory standardization relies on sustained efforts aligned with international quality benchmarks, such as ISO 15189, CAP, and EMQN. Further advancements in early detection and personalized treatment can be achieved by integrating emerging technological innovations within a robust QC framework, ultimately improving patient outcomes.

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АҢДАТПА

МОЛЕКУЛАЛЫҚ ГЕНЕТИКА ЗЕРТХАНАСЫНДАҒЫ САПАНЫ БАҚЫЛАУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Онкологиялық пациенттерде ерте диагностикалау мен болжамды бағалаудың тиімділігін арттыру үшін молекулалық биомаркерлерді анықтауды зертханалық жағдайларда сапаны қатаң бақылаумен біріктіру аса маңызды. Онкологиялық ауруларды зертханалық диагностикалауда дәлдік пен сапаны бақылау, нысаналы және дербестендірілген терапияны кеңінен енгізу аясында, ерекше мәнге ие болуда.*

Зерттеу мақсаты *– аналық без обырын диагностикалау мысалында молекулалық-генетикалық зертханаларда биомаркерді идентификациялау сапасын бақылауды бағалауға арналған жарияланымдарды шолу.*

Әдістері: *Осы зерттеу аясында жүргізілген жүйелі әдебиеттерге шолу 220 жазбаны анықтады, нәтижесінде 165 бірегей жарияланымдар алынды, оның ішінде 24 толық мәтінді мақала осы шолуға қосылды. Зерттеу жүйелі шолулар мен мета-талдаулар 2020 (PRISMA 2020) үшін артықшылықты есеп беру элементтері ұсынымдарына сәйкес жүргізілді.*

Нәтижелері: *Сапаны бақылау (Quality Control, QC) шараларын енгізу, соның ішінде калибрлеу, ішкі бақылау және біліктілікті тестілеу, Американдық патологтар колледжінің (CAP) ұсынымдарын пайдалана отырып жүргізілген жағдайда, қателіктердің санын айтарлықтай азайтады. Қаржыландырудағы шектеулерге қарамастан, Еуропалық молекулалық сапа желісі (EMQN) және CAP зертханалық тәжірибені галамдық деңгейде бағалауға бағытталған біліктілікті тестілеу бағдарламаларын ұсынады, бұл диагностикалық нәтижелердің үйлесімділігі мен сенімділігін қамтамасыз етеді.*

Қорытынды: *Клиникалық практикада молекулалық-генетикалық диагностикалық тесттердің дәлдігі мен сенімділігін қамтамасыз ету өте маңызды, әсіресе аналық без қатерлі ісігі сияқты ауруларда, онда нақты генетикалық талдау диагностикалық және емдеу стратегиясын анықтайды. Ерте диагностикалау мен дербестендірілген терапиядағы одан әрі жетістіктер жаңа технологиялық инновацияларды сенімді сапаны бақылау жүйесімен біріктіру арқылы жүзеге асырылуы мүмкін, бұл ақыр соңында пациенттерді емдеу нәтижелерін жақсартуға әкеледі. Осыған байланысты молекулалық-генетикалық тестілеудің, әсіресе аналық без қатерлі ісігін диагностикалауға арналған, стандартталған нұсқаулықтары мен стандартты операциялық процедураларын өзірлеу өзекті әрі қажетті міндет болып табылады.*

Түйінді сөздер: *Молекулалық-генетикалық тестілеу, сапаны бақылау (QC), BRCA1, BRCA2, полимеразалық тізбекті реакция (PCR), келесі ұрпақтың секвенирлеуі (NGS).*

АННОТАЦИЯ

КОНТРОЛЬ КАЧЕСТВА В ЛАБОРАТОРИИ МОЛЕКУЛЯРНОЙ ГЕНЕТИКИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Интеграция детекции молекулярных биомаркеров со строгим контролем качества в условиях лаборатории молекулярной генетики имеет ключевое значение для повышения эффективности ранней диагностики и оценки прогноза*

у онкологических пациентов. Точность и контроль качества в лабораторной диагностике онкологических заболеваний приобретают особую значимость в связи с широким внедрением таргетной и персонализированной терапии.

***Цель исследования** – обзор публикаций, посвященных оценке контроля качества идентификации биомаркеров в лабораториях молекулярной генетики на примере диагностики рака яичников.*

***Методы:** Систематический обзор литературы, проведенный в рамках данного исследования, выявил 220 записей, что привело к 165 уникальным публикациям, из которых 24 полнотекстовых статьи были включены в данный обзор. Исследование проводилось в соответствии с рекомендациями Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020).*

***Результаты:** Внедрение мер контроля качества (Quality Control, QC), включая калибровку, внутренний контроль и тестирование квалификации, используя рекомендации Колледжа американских патологов (CAP), существенно снижает количество ошибок, несмотря на сохраняющиеся ограничения в финансировании. Европейская молекулярная сеть качества (EMQN) совместно с CAP предлагают программы тестирования квалификации, направленные на оценку лабораторной практики в глобальном масштабе, обеспечивая согласованность и надежность результатов тестирования.*

***Заключение:** Обеспечение точности и надежности молекулярно-генетических диагностических тестов критически важно в клинической практике, особенно при заболеваниях, таких как рак яичников, где точный генетический анализ определяет стратегию диагностики и лечения. Дальнейшие достижения в раннем выявлении и персонализированной терапии могут быть достигнуты за счет интеграции новых технологических инноваций в рамках надежной системы контроля качества, что в конечном итоге приведет к улучшению результатов лечения пациентов. Следовательно, разработка стандартных руководств и стандартных операционных процедур для молекулярно-генетического тестирования, с особым акцентом на диагностику рака яичников, является насущной необходимостью.*

***Ключевые слова:** молекулярно-генетическое тестирование, контроль качества, BRCA1, BRCA2, полимеразная цепная реакция (ПЦР), секвенирование нового поколения (NGS).*

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INTRAOPERATIVE FLUORESCENT CONTRASTING FOR PRIMARY AND SECONDARY BRAIN TUMORS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Surgical resection of a brain tumor that is as radical and safe as possible remains an important step in the treatment of patients with primary and secondary brain tumors. It is difficult to distinguish tumor tissue from normal brain tissue during surgery using traditional white light microscopy. Intraoperative fluorescent contrast enhancement methods for brain tumors are used in real-time during the operation to overcome this limitation without disrupting the workflow. Several fluorescent drugs have been studied in recent decades, including 5-aminolevulinic acid (5-ALA), sodium fluorescein, and indocyanine green.*

The study aimed to *evaluate the experience of using intraoperative fluorescent contrast at the present and diagnostic capabilities, significance, application, and development prospects for primary and secondary brain tumors based on an analysis of literature data.*

Methods: *A systematic search of publications in the MEDLINE/PubMed database was performed using keywords related to the results of fluorescence contrasting in brain tumors with potential clinical significance.*

Results: *According to the literature review, 5-ALA has been the most studied drug among the listed fluorescent drugs. It is approved for use in different countries for intraoperative fluorescent contrast of grade III and IV malignancy glial tumors. Package Inserts do not indicate using 5-ALA to treat primary and secondary brain tumors of other histological structures or using sodium fluorescein and indocyanine green to treat brain tumors. However, the literature analysis demonstrates a large experience of their successful use.*

Conclusion: *Fluorescent contrast of primary and secondary brain tumors is a new, promising, and insufficiently studied method of visualizing brain tumor tissue during surgery in real time. Studying the possibilities and features of fluorescent contrasting primary and secondary brain tumors is a relevant and promising area of study, and its implementation in practice will improve treatment results.*

Keywords: *fluorescence-guided surgery, brain tumor; brain metastases, aminolaevulinic acid (5-ALA), sodium fluorescein, indocyanine green, fluorescence.*

Introduction: Treatment of malignant primary and secondary central nervous system (CNS) tumors is an urgent problem. According to the Register of Cancer Patients of Kazakh Institute of Oncology and Radiology (KazIOR, Almaty, Kazakhstan) for 2020-2023, the incidence of central nervous system malignant neoplasms (CNS MNs) in the Republic of Kazakhstan (RK) is about 800 new cases annually with an upward trend (815 cases in 2022) and reaches 4.0-4.2 cases per 100 thousand population. Mortality from CNS MNs in dynamics decreased from 2.1 per 100 thousand population (388 cases) in 2020 to 1.6 per 100 thousand population (320 cases) in 2023. Surgical treatment was performed on patients as monotherapy and as part of complex and combined treatment. In dynamics, there is an increase in the number of cases of surgical treatment performed from 69% in 2020 to 83.5% in 2023 [1, 2] (Figures 1-3).

A decrease in mortality from CNS MNs with increasing morbidity rates indicates an improvement in the quality of neuro-oncologic care in the Republic of Kazakhstan. The graphs show that the growth of neurosurgical care in combination with chemotherapy and radiation therapy plays an important role in achieving this. Improving the quality of neurosurgical care is a significant component of further improving the treatment outcomes in patients with primary and secondary brain tumors.

One of the main goals of neurosurgical intervention in brain neoplasms is the most possible radical and safe tumor resection. At the same time, the effectiveness of surgical intervention is limited by infiltrative tumor growth and the impossibility of total resection without damaging healthy brain tissue. As a result of damage to functionally significant areas of the brain, neurological deficits and disability of patients may develop, and in case of damage to vital areas - death. It is paramount to determine the extent of resection during surgery, especially at the border of the tumor and healthy tissue. The absence of a clear border characterizes infiltrative tumor growth. Differentiating tumor tissue from normal brain tissue during surgery using conventional white light microscopy is challenging. Intraoperative fluorescence contrast (IFC) techniques for tumors have been developed and used [3-28] to overcome this limitation.

The study aimed to evaluate the experience of using intraoperative fluorescence contrasting at the present stage, diagnostic capabilities, significance, application and development prospects in primary and secondary brain tumors based on the analysis of literature data.

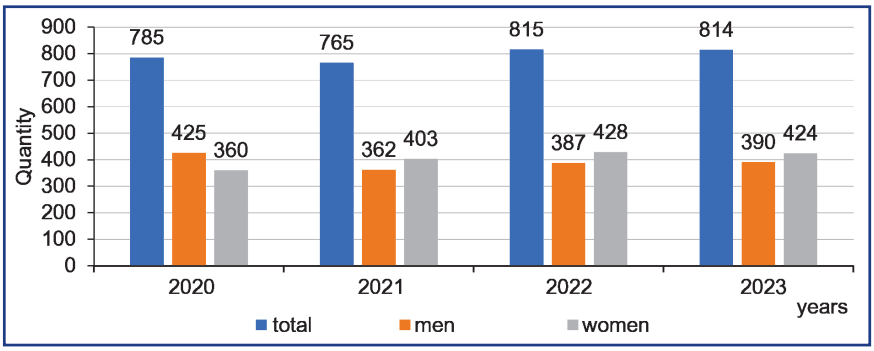

Figure 1 – Incidence of central nervous system malignant neoplasms in the Republic of Kazakhstan, 2020-2023 (4.0-4.2 cases per 100 thousand population), according to KazIOR Register

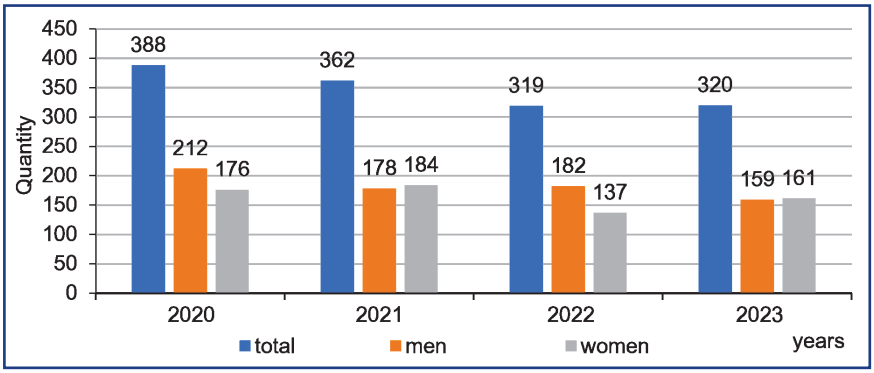

Figure 2 – Mortality from central nervous system malignant neoplasms in the Republic of Kazakhstan (1.6-2.1 cases per 100 thousand population), according to KazIOR Register

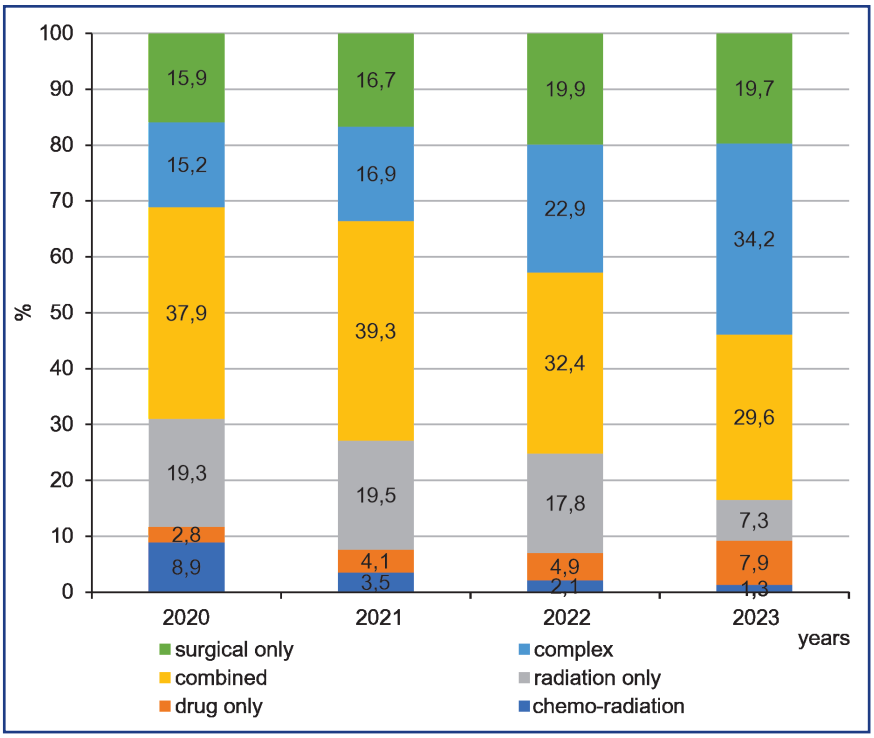

Figure 3 – Types of treatment for central nervous system malignant neoplasms in the Republic of Kazakhstan, 2020-2023, according to KazIOR Register

Materials and methods: We systematically searched publications from the MEDLINE/PubMed database using keywords related to fluorescence contrasting in brain tumors with potential clinical significance. Thirty-three publications were selected and analyzed for the study.

Results: The method of IFC of primary and secondary brain tumors is based on the ability of the fluores-

cent drug to accumulate in places of permeability violation of the blood-brain barrier (BBB) and tumor cells of the brain, as well as its ability to fluoresce when exposed to light of a certain wavelength. After a certain time, the drug is injected into the body, accumulating in the tumor tissue and on the border of the tumor in places of damaged BBB. Then, during surgery, the light of a certain wavelength causes luminescence (fluorescence) with the light of a different wavelength (a different color), contrasting tumor tissue against the background of healthy brain tissue.

IFC enables the surgeon to visualize the tumor tissue in real-time during surgery and perform the safest and most effective tumor resection possible. The amount of accumulated drug determines the fluorescence intensity and indicates the peculiarities of the histological structure and metabolism of the tumor [3, 5-18].

One of the side effects of using fluorescent drugs is photosensitization and phototoxicity, which can be used for therapeutic purposes, and intraoperative photodynamic therapy (PDT) can be performed. The concept of PDT is that the fluorescent agent accumulates in malignant cells, which become sensitized to exposure to visible light, and upon light exposure (during PDT), the tumor cells remaining in the infiltration zone after surgical resection die. In contrast, healthy and functionally important brain cells remain intact [7].

According to selected literature sources, fluorescent agents such as 5-aminolevulinic acid (5-ALA), Sodium Fluorescein (SF), and Indocyanine green (ICG) are used for IFC and visualization of primary and secondary brain tumors. The diagnostic capabilities, methodology, and features of using IFC to treat primary and secondary brain tumors are described.

5-ALA, SF, and ICG are considered safe and approved for use in many countries worldwide. However, according to the instructions for use, only 5-ALA is indicated for visualization of malignant glioma tissue (WHO grade III and IV). 5-ALA is registered in the Republic of Kazakhstan under the "Gliolan" trade name, reg. No. РК-ЛС-5 No. 024769 [19]. According to the user instructions, SF and ICG are used to study and assess blood flow in various organs, including the choroid of the eye and cerebral vessels, whereas their use for IFC of brain tumor tissue is not listed among the indications [20, 21]. SF and ICG are not registered in the Republic of Kazakhstan.

The conducted analysis of the literature revealed a sufficient number of publications on the effective use of IFC with 5-ALA, SF, and ICG in the treatment of primary and secondary brain tumors of various histological types, which show development potential and require further study and expansion of indications for use.

The available data on the use of 5-ALA in the treatment of primary and secondary brain tumors is based on biosynthesis and tumor selectivity: 5-ALA is a precursor of the fluorescent and phototoxic protoporphyrin IX (PpIX) in the heme biosynthesis pathway and is a natural metabolite of hemoglobin in the human body. When administered orally, 5-ALA crosses the blood-brain barrier (BBB) and the tumor-brain interface, is absorbed by malignant tumor cells, and is metabolized in the mitochondria into the fluorescent metabolite PpIX. Increased production and accumulation of PpIX in tumor cells allows for visualization of violet-red fluorescence of tumor tissue after excitation with blue light at a wavelength of 405 nm. [5, 6, 22].

Procedure: three to four hours before anesthesia, 5-ALA is dissolved in 50 ml of drinking water and administered orally at 20 mg/kg of body weight.

During surgery, at the tumor removal stage, a microscope with a light emission of 440 - 460 nm at 1% intensity is used for the IFC of the tumor. At the same time, tissues with areas of fluorescence of different intensities and colors can be visualized in real-time. In the presence of PpIX, red fluorescence will be observed with peaks at 635 and 705 nm. In the surgical field, one can observe with the naked eye the blue light with a wavelength of about 450 nm emitted by the excitation light source, green fluorescence from endogenous fluorophores, and red fluorescence caused by PpIX [3, 5-11, 14, 15, 22-29].

Based on the intraoperative real-time data of tumor fluorescence contrast, the surgeon visually identifies, by fluorescence intensity, areas with the highest density of tumor cells, healthy brain tissue, and the infiltration zone. This enables optimal decision-making regarding the extent of maximal possible tumor resection with minimal damage to functionally important brain tissue.

In cases of insufficient fluorescence intensity, the sensitivity of IFC of brain tumors using 5-ALA can be improved by reducing the intensity of the excitation blue light. For "non-fluorescent" tumors, more sensitive methods of PpIX detection, such as fluorescence spectroscopy, may be helpful [6].

Interpretation of IFC data for brain tumors using 5-ALA depends on fluorescence intensity. The amount of PpIX accumulation and the fluorescence intensity depends on the nature and type of tumor growth. Thus, "strong" fluorescence is most characteristic of solidly proliferating tumors with a high density of tumor cells, while "weak" fluorescence is typical of infiltrative tumors with moderate tumor cell density. The current IFC method can only characterize the fluorescence intensity but cannot make a quantitative assessment. Neurosurgeons usually distinguish three levels of fluorescence intensity: strong, uncertain (or weak), and no fluorescence, corresponding to solid tumor, infiltration zone, and normal brain, respectively [6, 7].

Despite the high diagnostic value of IFC, the possibility of false-positive and false-negative fluorescence must be considered. False-positive fluorescence may occur close to tumor cells; reactive astrocytes (e.g., radiation necrosis tissue) may produce false-positive fluorescence. In rare cases, autofluorescence of normal healthy

tissue may be observed. False-negative fluorescence may occur:

– in tumors with diffuse-infiltrative growth patterns in areas with low tumor cell infiltration density. In such cases, spectroscopy may be used to improve diagnostic accuracy. This is also observed in low-grade gliomas, which are usually not visualized using standard violet-blue light.

– in the presence of structural barriers interfering with visualization, such as blood, overhanging parts of healthy brain tissue, etc.;

– due to a bleaching effect — where fluorescence diminishes under exposure to blue light at 400 nm or standard white light. Bleaching up to 36% may occur after exposure to blue light for more than 25 minutes and over 87 minutes under standard white light;

– if surgery begins too early (less than 2 hours) or too late, false-negative fluorescence may occur since 5-ALA reaches its peak plasma concentration 4 hours after ingestion; however, sufficient fluorescence may still be observed even after 12 hours [6].

Features of surgery with 5-ALA:

– the patient receives not a fluorochrome but its non-fluorescent precursor, which ensures higher contrast between tumor cells and healthy brain tissue due to the absence of nonspecific background fluorescence associated with fluorescent agents in the blood and interstitial space;

– there is selective accumulation of PpIX in tumor tissue at the cellular level;

– to prevent functional neurological deficits after surgery, functionally important brain areas potentially infiltrated by malignant cells must be considered, and once functioning brain areas are detected, tumor resection must be discontinued, even in the presence of fluorescence;

– it is necessary to dim the lights to avoid reflections that could be mistaken for PpIX fluorescence [6, 7].

Experience with the use of 5-ALA for IFC of primary and secondary brain tumors according to literature data: According to its instructions for use, 5-ALA is indicated for IFC of WHO grade III or IV gliomas; however, literature analysis shows that 5-ALA is also successfully used for IFC of primary and secondary brain tumors of other histological types [6 - 9].

R. Díez Valle *et al.* (2019) analyzed more than 300 articles on 5-ALA use and concluded that IFC of high-grade gliomas is a reliable and reproducible method that can influence the extent of tumor resection and patient outcomes. At the same time, IFC with 5-ALA for other tumor types requires further development [24].

H.A. Shah *et al.* (2022) conducted a systematic review on using 5-ALA for fluorescence-guided resection of brain metastases. Based on the analysis of 10 selected studies involving 631 patients, they noted that 5-ALA fluorescence rates for brain metastases ranged from 27.6% to 86.9%, depending on tumor type variability. None of the studies concluded that using 5-ALA improved surgical outcomes or survival. It has been concluded that current studies on using 5-ALA for brain metastases are limited and do not confirm the effectiveness in improving the extent of resection or postoperative survival and that fluorescence intensity varies depending on the tumor type. They highlight the need for further investigation into the benefits of IFC using 5-ALA for specific histological tumor types and the study of the diagnostic value of quantitative fluorescence assessment [23].

Based on data from 19 publications covering 175 surgeries performed under 5-ALA fluorescence guidance in pediatric tumors, M. Schwake *et al.* (2019) noted that this technique facilitates tumor identification during surgery and was useful in 78% of glioblastomas, 71% of WHO grade III anaplastic ependymomas, while its usefulness in pilocytic astrocytomas and medulloblastomas was lower - 12% and 22%, respectively [9].

F. Marhold *et al.* (2022) studied 29 cases of 5-ALA fluorescence contrast in brain melanoma metastases. Visible fluorescence was observed in only 28% of cases, while in 72%, it was absent. Analysis showed that the presence or absence of fluorescence was not associated with the degree of pigmentation, intratumoral hemosiderin, or hemorrhage [25].

Despite the low diagnostic value of 5-ALA fluorescence contrast in brain melanoma metastases, in the study by J. Takahashi *et al.* (2019), the therapeutic effectiveness of 5-ALA in PDT for brain melanoma metastases was demonstrated in an experimental setting [26].

M.A. Kamp *et al.* (2016) analyzed 84 cases of 5-ALA fluorescence contrast in brain metastases. Strong or weak fluorescence was noted in 40.5% of cases, while in 59.5%, no fluorescence was observed. The primary site and histological type of metastasis did not correlate with fluorescence behavior. A significant correlation was found between 5-ALA fluorescence and the local tumor progression rate in the brain. Patients with 5-ALA-negative metastases had a higher risk of local recurrence compared to 5-ALA-positive metastases [28].

In 2019, A. Boschi and A. Della Puppa conducted a literature review on using 5-ALA for IFC of brain tumors and concluded that this agent may be beneficial not only for WHO grade III and IV gliomas but also for tumors of other histological types. High efficacy was noted in low-grade gliomas with areas of anaplasia, meningiomas with parenchymal infiltration or skull bone invasion, ependymomas, lymphomas, and pediatric tumors [30].

Thus, despite mixed results in the use of 5-ALA in the treatment of low-grade gliomas and brain metastases, authors agree that this issue requires further investigation into the diagnostic value of the method for tumors of different histological types [5, 7, 9, 22, 25, 27, 29-31]. They point to the potential for expanding the application in cases of negative fluorescence by using more sensitive fluorescence detection methods [6, 7, 10]. The potential for the therapeutic use of 5-ALA in photodynamic therapy is also emphasized separately [7, 26].

The literature analysis showed that 5-ALA, SF, and ICG are also used for fluorescence contrast of brain tumors [12 - 18, 27, 30, 31].

Currently, it is believed that SF and ICG penetrate and accumulate in the intercellular space in areas of the brain where the BBB is disrupted, which allows visualization of tumor margins during fluorescence imaging, similar to the contrast enhancement observed with gadolinium-enhanced MRI [12, 14, 15, 17]. Lower cost compared to 5-ALA, non-toxicity, ease of use (intravenous administration during surgery), and a wide range of diagnostic capabilities covering all contrast-enhancing brain lesions with BBB disruption are reasons for the growing interest in using these fluorochromes for IFC in the treatment of primary and secondary brain tumors [12 - 18].

SF is excited by light at 460 - 500 nm wavelength and fluoresces green at 540 - 690 nm. A visual representation of glioblastoma under fluorescence contrast using 5-ALA and SF is shown in Figure 4 [14].

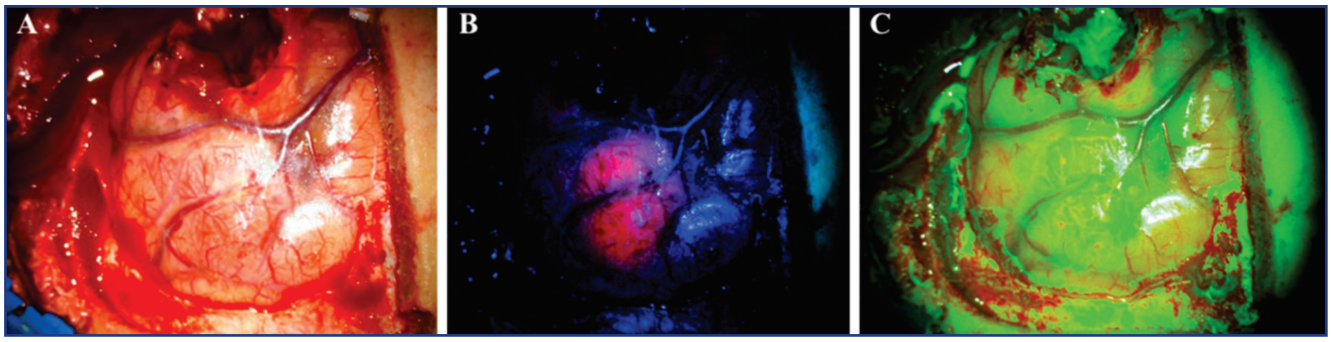

Figure 4 – View of tumor and healthy tissue during intraoperative fluorescence contrast of glioblastoma: A – under white light; B – under blue light with 5-ALA, red glow on a blue background is observed; C – under yellow light with Sodium Fluorescein, the tumor glows green on a yellow background [14].

SF is administered intravenously during anesthesia before surgery, after which the agent accumulates in areas of BBB disruption, and fluorescence can be visualized within 4 hours after injection [14, 18]. Previously, SF was used for fluorescence at high doses (20 mg/kg) and visualized under an operating microscope using white light. Using a special yellow filter with excitation light at a wavelength of 560 nm allowed for increased sensitivity and reduction of the dose to 3 - 5 mg/kg, administered before surgery [14, 18].

L.C. Ahrens *et al.* (2022) presented an analysis of data on the use of fluorescence with 5-ALA and SF, concluding that SF can be a viable alternative to 5-ALA for surgical removal of high-grade gliomas. Moreover, SF is useful for fluorescence-guided visualization of many primary and secondary brain tumors, including metastases, and has several advantages over 5-ALA, such as a broader application spectrum, lower cost, and easier administration. The authors emphasize the need for further research [14].

B. Musca *et al.* (2023) revealed in their study that SF not only accumulates in areas of BBB disruption in the intercellular space but is also absorbed intracellularly by tumor and immune cells [12].

A. Narducci *et al.* (2023), based on a study of 48 patients with suspected high-grade glioma who underwent stereotactic biopsy with SF fluorescence contrast, demonstrated the utility of this method, which increased the accuracy of tissue sampling by 13.8% compared to the non-fluorescence method while reducing the average number of biopsy samples from 4.4 to 3.3 [31].

In their review of 23 cases of brain tumor lesions that showed gadolinium enhancement on MRI and stereotactic biopsies with SF contrast (93 samples), D.K. Singh *et al.* (2021) proposed SF fluorescence as a convenient tool for stereotactic brain tumor biopsies that can improve diagnostic accuracy [32].

ICG is a water-soluble dye approved by the FDA for biomedical purposes. Due to its fluorescence in the near-infrared (NIR) spectrum, it is widely used in medical applications. Its maximum light absorption occurs in the infrared range at 800 nm (778 - 806 nm), with peak emission measured by fluorescence at 830 nm and peak radiation at 835 nm in biological tissues. ICG fluorescence emission in the NIR range has a greater tissue penetration depth of up to 15 mm, whereas visible-light fluorophores penetrate up to 3 mm. In addition, NIR fluorescence with ICG is less affected by autofluorescence since biological tissue generally does not emit fluorescence in the NIR spectrum. In the early 2000s, ICG was officially introduced into neurosurgical practice as an intraoperative cerebrovascular contrast agent for brain vessel imaging (video angiography). In 2016, a group of authors developed a new technique called "Second Window Indocyanine Green" (SWIG), which involves the infusion of a high dose of ICG (5.0 mg/kg) 24 hours before surgery. ICG acts as a passive targeting agent and accumulates in areas with BBB disruption and in tumor tissue. Unlike 5-ALA and SF, ICG is a NIR fluorophore, which provides higher resolution with deeper tissue penetration [15 - 18, 33]. An example of ICG fluorescence visualization is shown in Figure 5 [16].

As an infrared fluorochrome, ICG has advantages over other fluorochromes currently operating in the visible spectrum due to the increased tissue penetration of

NIR fluorescence and reduced autofluorescence. According to reviewed sources, SWIG has been used in patients with high-grade gliomas, meningiomas, brain metastases, pituitary adenomas, craniopharyngiomas, chordomas, and pineal region tumors [15 - 18, 33]. This indicates the promising potential for further study and broader application of ICG in treating primary and secondary brain tumors.

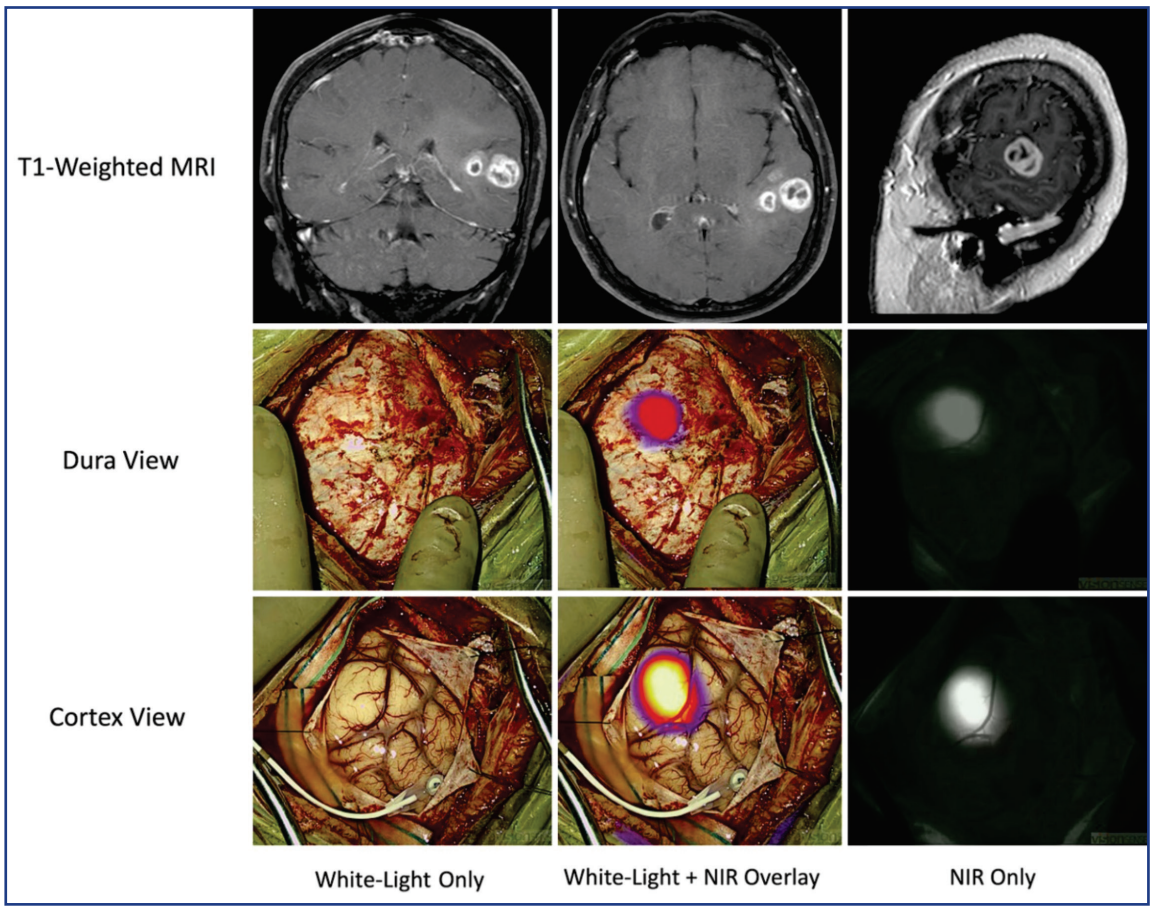

Figure 5 – The top row shows MRI scans of a patient with glioblastoma multiforme in T1-weighted contrast-enhanced mode (T1-Weighted MRI). The second and third rows show images under white light only and during fluoroscopy using the Second Window ICG under white light combined with infrared imaging (White-Light + NIR Overlay) and under infrared only (NIR Only). The second and third rows present images before (Dura View) and after durotomy (Cortex View) [16].

Discussion: Maximally radical and safe surgical resection of brain tumors remains a crucial stage in the treatment of patients with primary and secondary brain tumors. Differentiating tumor tissue from normal brain tissue during surgery using conventional white light microscopy is challenging. Real-time implementation of IFC methods without interrupting the surgical process allows us to overcome this limitation. Over the past decades, several fluorescent agents have been studied, including 5-ALA, SF, and ICG [11].

According to the literature review, among these agents, 5-ALA is the most extensively studied and approved for use in IFC of WHO grade III and IV gliomas, as reflected in the instructions for use. The instructions do not indicate the use of 5-ALA for treating primary and secondary brain tumors of other histological types. Similarly, SF and ICG are not indicated for the treatment of brain tumors according to their respective instructions for use. However, the literature review revealed substantial clinical experience demonstrating their successful application [3, 5 - 33].

Takeaways:

– IFC of primary and secondary brain tumors is an effective tool for real-time visualization of tumor tissue, which expands the surgeon's capabilities during the procedure, enables the selection of the most optimal resection volume, and thereby improves the quality of surgeries and treatment outcomes;

– The data from the literature review demonstrate the high diagnostic value of IFC for high-grade gliomas using 5-ALA, which is recommended for implementation and use in clinical practice, as reflected in the instructions for use. Expanding the indications for the use of 5-ALA for intraoperative contrast of primary and secondary brain tumors of other histological types is promising and insufficiently studied;

– The extension of current indications of SF and ICG for fluorescence-guided contrast imaging of primary

and secondary brain tumors is promising and necessary for improving the quality of treatment of CNS neoplasms;

– Intraoperative use of fluorescent agents expands not only the diagnostic capabilities of the surgeon but also the therapeutic potential for treating primary and secondary brain tumors through photodynamic therapy, although this method requires further study before clinical implementation.

Conclusion: According to the literature review, fluorescence-guided contrast imaging of primary and secondary brain tumors is a novel, promising, and insufficiently studied method of visualizing tumor tissue and the brain during real-time surgery. In addition to its diagnostic value, the use of fluorescent agents also has a therapeutic effect when performing intraoperative PDT.

Thus, the study of the potential and specific features of fluorescence-guided contrast imaging for primary and secondary brain tumors is a relevant and promising area of research, and its implementation into practice could improve treatment outcomes.

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АҢДАТПА

АЛҒАШҚЫ ЖӘНЕ ЕКІНШІЛІК МИ ІСІКТЕРІН ИНТРАОПЕРАЦИЯЛЫҚ ФЛУОРЕСЦЕНТТІК КОНТРАСТТАУ: ӘДЕБИ ШОЛУ

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Өзектілігі: *Ми ісігінің ең радикалды және қауіпсіз хирургиялық резекциясы бас миының бастапқы және қайталама ісіктері бар науқастарды емдеудегі маңызды қадам болып қала береді. Дәстүрлі ақ жарық микроскопиясын қолданып операция кезінде ісік тінін қалыпты ми тінінен ажырату қиын. Бұл шектеуді еңсеру үшін операция кезінде нақты уақыт режимінде және жұмыс процесін бұзбай, ми ісіктерін интраоперациялық флуоресцентті контрастты күшейту әдістері қолданылады. Соңғы онжылдықтарда бірнеше флуоресцентті препараттар зерттелді, соның ішінде 5-аминолевулин қышқылы (5-ALA), натрий флуоресцеин және жасыл индоцианин.*

Мақсат: *Әдебиет деректерін талдау негізінде қазіргі кезеңде интраоперациялық флуоресцентті контрастты қолдану тәжірибесін, диагностикалық мүмкіндіктерін, маңызын, біріншілік және қайталама ми ісіктерін қолдану және даму перспективаларын бағалау.*

Әдістері: *MEDLINE/PubMed деректер базасын жүйелі іздеу ықтимал клиникалық маңызы бар ми ісіктері кезіндегі флуоресценциялық контраст нәтижелеріне қатысты түйінді сөздерді пайдалана отырып жүргізілді.*

Нәтижелері: *Әдебиеттік шолуға сәйкес, аталған препараттардың ішінде 5-аминолевулин қышқылы ең көп зерттелгені және әлемнің әртүрлі елдерінде III және IV дәрежелі қатерлі ісіктердің глиальды ісіктерінің интраоперациялық флуоресцентті*

контрастын қолдану үшін рұқсат етілгені анық. Басқа гистологиялық құрылымдардың бастапқы және қайталама ми ісіктерін емдеу үшін 5-ALA қолдану нұсқаулықта көрсетілмеген, сонымен қатар натрий флуоресцеинін және индоцианин жасылын қолдану жөніндегі нұсқаулықта емдеуде қолдануға көрсеткіштер жоқ; ми ісіктері, ал әдебиет деректерін талдау оларды сәтті қолданудың үлкен тәжірибесін көрсетті.

Қорытынды: *Бастапқы және қайталама ми ісіктерінің флуоресценциялық контрастты бейнелеуі операция кезінде мидың нақты уақыт режимінде бейнеленуінің жаңа перспективалы және аз зерттелген әдісі болып табылады. Бастапқы және қайталама ми ісіктерінің флуоресценттті контрастын қолдану мүмкіндіктері мен ерекшеліктерін зерттеу өзекті және перспективалық зерттеу бағыты болып табылады және оны тәжірибеге енгізу емдеу нәтижелерін жақсартады.*

Түйінді сөздер: *флуоресценциямен басқарылатын хирургия; ми ісігі; мидағы метастаздар; аминолевулин қышқылы (5-ALA); натрий флуоресцеин; индоцианин жасыл; флуоресценция.*

АННОТАЦИЯ

ИНТРАОПЕРАЦИОННОЕ ФЛУОРЕСЦЕНТНОЕ КОН-ТРАСТИРОВАНИЕ ПРИ ПЕРВИЧНЫХ И ВТОРИЧНЫХ ОПУХОЛЯХ ГОЛОВНОГО МОЗГА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Максимально возможное удаление опухолевой ткани с сохранением функционально значимых участков головного мозга остается одной из основных целей хирургического удаления первичных и вторичных опухолей головного мозга. Отличить опухолевую ткань от нормальной ткани мозга во время операции с использованием традиционной микроскопии в белом свете затруднительно. Для преодоления этого ограничения используются методы интраоперационного флуоресцентного контрастирования опухолей головного мозга с использованием флуоресцентных препаратов. Наиболее изученными флуоресцентными препаратами являются 5-аминолевулиновая кислота, Флуоресцеин натрия и Индоцианин зеленый.*

Цель исследования *– оценить опыт использования интраоперационного флюоресцентного контрастирования на современном этапе, диагностические возможности, значение, применение и перспективы развития при первичных и вторичных опухолях головного мозга на основании анализа литературных данных.*

Методы: *Проведен системный поиск публикаций из базы данных MEDLINE/PubMed по ключевым словам, связанным с результатами применения флюоресцентного контрастирования при опухолях головного мозга, которые имеют потенциальное клиническое значение. Для исследования выбрано и проанализировано 33 публикации.*

Результаты: *По данным проведенного литературного обзора видно, что из перечисленных флуоресцентных препаратов 5-аминолевулиновая кислота наиболее изучена и одобрена к применению для интраоперационного флуоресцентного контрастирования глиальных опухолей III и IV степени злокачественности, что отражено в инструкции по применению препарата. Использование 5-аминолевулиновой кислоты для лечения первичных и вторичных опухолей головного мозга другой гистологической структуры в инструкции по применению не указаны, также в инструкции по применению Флуоресцеина натрия и Индоцианина зеленого нет показаний для применения при лечении опухолей головного мозга, тогда как проведенный анализ литературных данных показал большой опыт их успешного применения.*

Заключение: *Флуоресцентное контрастирование первичных и вторичных опухолей головного мозга является новым перспективным и недостаточно изученным методом визуализации опухолевой ткани и мозга во время операции в режиме реального времени. Изучение возможностей и особенностей применения флуоресцентного контрастирования первичных и вторичных опухолей головного мозга является актуальным и перспективным направлением в изучении, а его внедрение в практику позволит улучшить результаты лечения.*

Ключевые слова: *хирургия под флуоресцентным контролем, опухоль головного мозга, метастазы в головной мозг, аминолевулиновая кислота (5-ALA), Флуоресцеин натрия (FS), Индоцианин зеленый (ICG), флуоресценция.*

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REHABILITATION STRATEGIES FOR PATIENTS WITH SARCOMAS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Due to modern treatment methods, sarcoma patients' survival rate is increasing. Rehabilitation helps to minimize physical and functional limitations caused by aggressive therapy, improves mental health, and promotes social and professional adaptation. Since sarcoma predominantly affects working-age people, rehabilitation plays a key role in restoring body functions, improving the quality of life, and reintegrating patients into society.*

The study aimed to *analyze the scientific literature on modern approaches to rehabilitating sarcoma patients.*

Methods: *A search and selection of articles were conducted in the Pubmed, Web of Science, Scopus, and RSCI databases using the main keywords and phrases: «orthopedic oncology,» «sarcoma,» «rehabilitation,» and «rehabilitation strategies.» The review included articles published within the last 10 years relevant to the topic. Case reports, correspondence, letters, and studies not conducted on humans were excluded from the review.*

Results: *The article presents data on selecting the most effective rehabilitation technologies for sarcoma patients and provides arguments for implementing new approaches and methods into clinical practice. Rehabilitation is divided into several main types: medical (which involves physiotherapy, the use of medications, etc.), physical (based on the restoration of the range of motor functions, coordination, and strength), psychological (includes work on the patient's psycho-emotional state), social (implies the patient's return to social activity, assistance in the adaptation period), rehabilitation using modern technologies (assistance from robotic systems, computer simulation of augmented virtual reality, the use of smartwatches and fitness bracelets).*

Individually selected and adapted rehabilitation concepts within a multidisciplinary and interdisciplinary setting are essential for optimizing function in patients with sarcoma.

Conclusion: *Rehabilitation of patients with sarcoma is not only a medical but also a social task. Successful recovery of patients contributes to their full return to active life, which is of critical social importance.*

Keywords: *sarcoma, rehabilitation, multidisciplinary approach, modern rehabilitation technologies.*

Introduction: Currently, sarcomas account for about 1% of all malignant neoplasms in adults and 15% in children and adolescents. Sarcomas are characterized by rapid growth, propensity to metastasize, and high risk of recurrence, which complicates prognosis and requires regular follow-up. Treatment of sarcomas often involves surgery, including amputations or extensive resections, as well as the use of chemotherapy, radiation, and beam therapy, which is often accompanied by serious physical and psychological consequences that significantly reduce the quality of life of patients and require special attention.

According to the Kazakh Research Institute of Oncology and Radiology (hereinafter referred to as KazNIIOIR, Almaty, Kazakhstan), in 2023, the incidence of sarcomas amounted to 0.9% of all malignant neoplasms. There were 1,250 new cases, of which 60% were soft tissue sarcomas and 40% were bone sarcomas [1].

The most common sarcomas are osteosarcoma, chondrosarcoma, and Ewing sarcoma. The five-year survival rate varies depending on the type of sarcoma and the stage of the disease: in the early stages, the survival rate can reach 70-80%, while in advanced stages it decreases to 20-30% [2, 3].

Modern treatment methods, such as targeted therapies and improved surgical approaches, help improve the survival of patients with sarcomas but increase the number of patients requiring long-term rehabilitation [3, 4].

Motor difficulties, chronic and phantom pain, and psychological disorders, including depression and anxiety, may occur after treatment. Since sarcomas most often occur in working-age people, rehabilitation plays a key role in restoring body function, improving quality of life, and minimizing the effects of aggressive treatment.

Numerous studies have confirmed the need for restorative treatment immediately after surgery in orthopedic oncologic patients. Lack of timely comprehensive rehabilitation often leads to unsatisfactory functional

outcomes. Full rehabilitation significantly improves functional performance. Regardless of the nature of the surgical intervention (including mutilation), the patient's functional activity level is a key factor affecting quality of life. Among the main tasks of rehabilitation of sarcoma patients are their early activation, contributing to the stabilization of hemodynamics, and prevention of cardiopulmonary, thrombotic, and other postoperative complications, including those caused by prolonged immobilization. Moreover, rehabilitation is aimed at preparing patients for upright posture and learning to walk. After organ-preserving surgeries in orthopedic oncology, there is a significant association between mobility limitation in the operated joints, functional indices, and quality of life of patients [5-9].

Rehabilitation of cancer patients should begin as early as possible and continue throughout life.

The study aimed to analyze the scientific literature on modern approaches to rehabilitating sarcoma patients.

Materials and Methods: The search and selection of articles in Pubmed, Web of Science, Scopus, and RINC databases by main keywords and word combinations were carried out: "orthopedic oncology," "sarcoma," "rehabilitation," and "rehabilitation strategies." The review included articles no more than 10 years old that were relevant to the subject of this review. Case reports, correspondence, letters, and studies not conducted on humans were excluded from the review.

Results: Rehabilitation in orthopedic oncology is a branch of medicine that continues to improve in line with advances in cancer science.

This article summarizes the existing literature on sarcoma rehabilitation and provides a comprehensive review of the effects of various rehabilitation interventions that can be used as a basis for individualized rehabilitation in clinical practice.

It is important to note that the number of scientific studies on sarcoma patients' rehabilitation is small.

In recent years, there has been increased recognition of the importance of rehabilitation in optimizing function in sarcoma patients [10]. Rehabilitation should be comprehensive [11]. A multidisciplinary rehabilitation team may include a physical therapist, nurse, occupational therapist, speech therapist, orthopedist, prosthetist, social worker, psychologist, and dietitian [12]. Although people may not need all these services, they should be available wherever cancer care is provided.

A multidisciplinary rehabilitation plan can help minimize symptoms and sequellae that adversely affect a patient's function and quality of life, including chemotherapy-induced pain, peripheral neuropathy, radiation fibrosis, activity limitations after surgical removal, amputation, bowel and bladder dysfunction, and lymphedema.

Rehabilitation prior to cancer treatment, known as pre-rehabilitation, may help to increase tolerance to toxic and harmful side effects [13]. And while pre-rehabilitation can potentially improve chemotherapy tolerance, a key component of pre-treatment rehabilitation is patient counseling. If a choice must be made between limb salvage and amputation, patients should be fully informed of the advantages and disadvantages of each procedure, including potential functional deficits.

Immediately after surgery, patients can benefit from inpatient rehabilitation.

Patients who undergo amputation due to sarcoma have been shown to make significant progress during inpatient rehabilitation compared to a control group with a dysvascular lesion, with the majority being discharged home [14]. The goal of rehabilitation at this stage is primarily to strengthen the patient and provide adaptive equipment and strategies to address functional deficits for a safe discharge home. It includes physiotherapy, medication, physical therapy (PT), massage, ultrasound therapy and electrophoresis. It is known that physical therapy is characterized by certain criteria such as frequency, intensity, and type (e.g., strengthening, endurance, and functional exercises) [15]. Exercises affect functional impairment by improving balance, muscle strength, and endurance, relieving cancer-related fatigue, and enhancing physical abilities [16]. It is believed that exercises increase patients' self-confidence and stabilize psychological well-being. When choosing this rehabilitation, patients face several limitations, such as a limited number of specialized centers, especially in remote regions, and a lack of qualified specialists with experience in working with cancer patients. It was essential to recall individual limitations, which can significantly limit the choice of rehabilitation methods.

For cancer patients, psychological problems begin at the time of diagnosis, so the earlier psychological rehabilitation begins, the better it will be for the patient and his/her family members.

A mental health professional with expertise in functional loss and chronic illness is an invaluable member of the interdisciplinary team for many cancer patients. Cancer diagnosis and treatment can be a traumatic experience that patients tolerate differently, and patients undergoing sarcoma treatment are at increased risk of developing anxiety, depression, and adjustment disorders associated with grief from the loss of a limb [17].

This is true for all stages of the disease, including survival. In addition, patients with sarcoma are at increased risk of suicide [18].

Psychological support programs may include individual and group therapy with psychologists and psychotherapists [19, 20].

One of the important rehabilitation aspects is the return to an active social life, which includes vocational rehabilitation programs to help patients return to work or school [21], help with social adjustment, devel-

opment of social skills, and support in returning to an active life.

Helping patients return to school and work is also vital for restoring quality of life after sarcoma treatment. Returning to ordinary activities can improve the sense of well-being. Children and adolescents may require individualized learning plans in the short term after returning to school. For adults, perceptions of the employer's work environment are particularly important, and doctors play a crucial role in guiding any necessary changes in the workplace [22]. The patient's expected job duties should be listed, and guidelines should be provided for activities that can and cannot be performed. Any return to school or work after significant cancer treatment should be gradual and flexible, creating an opportunity for the patient to adjust to normal routines.

Not everyone can undergo inpatient rehabilitation, as not all hospitals, especially in remote regions, provide rehabilitation for cancer patients. Telemedicine has allowed online consultations with doctors, prescribing PT programs, and monitoring their implementation [11].

The telerehabilitation system allows a patient to consult with doctors and rehabilitate from any place with internet access. It also helps to save money and time to reach a rehabilitation center or hospital.

The development of modern medical technologies has allowed for the improvement of not only the methods of sarcoma treatment but also the methods of sarcoma patients' rehabilitation. Innovative methods accelerate recovery, improve accuracy in diagnosing complications, and improve patients' quality of life.

Robotic systems are now used to restore motor activity in patients after amputation or major surgery. For example, exoskeletons [23, 24] help patients with limited mobility strengthen muscles and learn to control prosthetic limbs and robotic simulators such as Lokomat et al. are used to restore gait and coordination.

3D technology is gradually introduced into rehabilitation. 3D printing is increasingly used to create customized prostheses and orthoses, which is especially important for patients with non-standard anatomy after tumor resection [20, 25].

Virtual reality technologies help rehabilitate motor functions, improve the skill of using a bionic prosthesis, and relieve pain. For example, virtual reality training helps patients restore motor function through interactive exercises [11, 26].

Rehabilitation methods currently include the use of modern technology, such as the use of fitness bracelets and smart watches to monitor vital signs and activity levels.

The implementation of artificial intelligence tools is actively promoted to analyze patient data, modify the rehabilitation plan according to the needs, and create personalized treatment programs based on the patient's clinical data [14].

Discussion: Integration of a multidisciplinary approach is one of the important modern approaches in rehabilitation. A multidisciplinary team is required for more effective rehabilitation, especially for oncological diseases. Oncologists, surgeons, rehabilitation therapists, physical therapists, psychologists, and social workers can be considered the main specialists of the team. The teamwork of these specialists is based primarily on the construction of an individualized rehabilitation plan.

Rehabilitation of patients with limb sarcomas is challenging, and the approach varies depending on the choice of surgical procedure as well as potentially associated medical complications [27]. Therefore, finding a way to adapt to a new life situation and return to work is a complex but important task for both the individual and society. It is also well known that rehabilitation needs after treatment vary considerably from one person to another [22].

An individualized rehabilitation plan is necessary to consider the patient's characteristics, such as the type and localization of sarcoma, the amount and nature of treatment received, age, gender, physical and psychological condition, allowing creation of the rehabilitation plan according to the patient's individual needs. This approach will allow for tracking the progress, making adjustments, and providing better rehabilitation.

Despite significant advances and modern medical technology, the rehabilitation field has limitations. The high cost of equipment such as exoskeletons and robotic systems limits availability. Specially trained specialists must effectively use technology; their training requires separate costs. Not all patients, especially older patients, can adapt to new technologies and rehabilitation methods. Ensuring that all the necessary specialists are available in one place is not always possible. Overloading the patient with various recommendations and procedures and possible contradictions in the approaches of different specialists can reduce the effectiveness of rehabilitation. Problems with integrating methods and the time dependency of organizing appointments and coordinating treatment can also slow patient recovery, making a multidisciplinary approach challenging in some situations.

In modern Kazakhstan, ensuring effective rehabilitation and improving palliative care for cancer patients is one of the objectives of the Comprehensive Plan to Combat Cancer in the Republic of Kazakhstan for 2023-2027 [28]. In this regard, introducing modern, proven practices in the system of rehabilitation of sarcoma patients in Kazakhstan is one of the important steps for the successful recovery of patients and ensuring a full quality of life.

The health of the working-age population is of great importance to society. Therefore, rehabilitation of sarcoma patients, which affects a predominantly working-age population, is not only a medical but also a social challenge. Successful recovery is an opportunity for

patients to return to an active life and reintegrate back into society.

Conclusion: Data on the complex rehabilitation measures for sarcomas are insufficient in the literature. The gap between rehabilitation studies and practice requires further action focused on disseminating and implementing available research findings. This review deepens the knowledge base by providing a comprehensive analysis of the effectiveness of these interventions.

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АҢДАТПА

САРКОМАСЫ БАР ПАЦИЕНТТЕРГЕ АРНАЛҒАН РЕАБИЛИТАЦИЯ СТРАТЕГИЯЛАРЫ: ӘДЕБИЕТТЕРГЕ ШОЛУ

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Өзектілігі: *Заманауи емдеу әдістерінің арқасында саркомасы бар науқастардың өмір сүру деңгейі артады. Реабилитация агрессивті терапиядан туындаған физикалық және функционалдық шектеулерді азайтуға көмектеседі, психикалық денсаулықты жақсартады, әлеуметтік және кәсіби бейімделуге ықпал етеді. Саркома көбінесе еңбекке қабілетті жастағы адамдарға әсер ететінін ескере отырып, реабилитация дене функцияларын қалпына келтіруде, өмір сапасын жақсартуда және қоғамға оралуда шешуші рөл атқарады.*

Зерттеудің мақсаты *саркомасы бар науқастарды реабилитацияның заманауи тәсілдері туралы ғылыми әдебиеттерді талдау болып табылады.*

Материалдары мен әдістері: *Pubmed, Web of Science, Scopus және РҒДИ дерекқорларында «онко-ортопедия», «саркома», «реабилитация», «реабилитация шаралары» сияқты негізгі түйінді сөздер мен сөз тіркестерін пайдаланып мақалаларды іздеу және таңдау жүргізілді. Шолу 10 жылдан аспайтын осы шолудың тақырыбына қатысты мақалаларды қамтыды. Бір реттік бақылау есептері, корреспонденциялар, хаттар және адамдарда жүргізілмеген зерттеулер шолуға қосылмаған.*

Нәтижелері: *Мақалада саркомасы бар науқастардың реабилитациясының ең тиімді технологияларын таңдауға қатысты деректер және жаңа тәсілдер мен әдістерді тәжірибеге енгізу бойынша ұсыныстарға қатысты дәлелдер келтірілді. Реабилитация бірнеше негізгі түрге бөлінеді: медициналық (физиотерапия жүргізу, дәрі-дәрмектер қолдану және т.б.), физикалық (қозғалыс функцияларын, үйлестіруді, күшті қалпына келтіруге негізделген), психологиялық (науқастың психоэмоционалдық жағдайымен жұмыс істеуді қамтиды), әлеуметтік (науқастың әлеуметтік белсенділікке оралуын, бейімделу кезеңінде көмек көрсетуді білдіреді), заманауи технологияларды пайдалану арқылы жүргізілетін реабилитация (роботтандырылған жүйелердің көмегі, толықтырылған виртуалды шындық компьютерлік симуляциясы, ақылды сағаттар мен фитнес-білезіктерді қолдану).*

Саркомасы бар науқастарда функцияны оңтайландыру үшін көпсалалы және пәнаралық тәсіл аясында жеке таңдалған және бейімделген реабилитация концепциялары маңызды рөл атқарады.

Қорытынды: *Саркомасы бар науқастардың реабилитациясы тек медициналық ғана емес, сонымен қатар әлеуметтік міндет болып табылады. Науқастардың табысты сауығуы олардың белсенді өмірге толық оралуына ықпал етеді, бұл жалпы қоғам үшін үлкен маңызға ие.*

Түйінді сөздер: *саркома, реабилитация, мультидисциплинарлық тәсіл, реабилитациядағы заманауи технологиялар.*

АННОТАЦИЯ

СТРАТЕГИИ РЕАБИЛИТАЦИИ ПАЦИЕНТОВ С САРКОМАМИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Благодаря современным методам лечения увеличивается выживаемость пациентов с саркомой. Реабилитация помогает минимизировать физические и функциональные ограничения, вызванные агрессивной терапией,*

улучшает психическое здоровье, способствует социальной и профессиональной адаптации. Учитывая, что саркома чаще всего приходится на людей трудоспособного возраста, реабилитация играет ключевую роль в восстановлении функций организма, улучшении качества жизни и возвращение в общество.

***Цель исследования** – анализ научных публикаций о современных подходах к реабилитации пациентов с саркомой.*

***Методы:** Был проведен поиск и отбор статей в базах данных Pubmed, Web of Science, Scopus, РИНЦ по основным ключевым словам и словосочетаниям: «онкоортопедия», «саркома», «реабилитация», «реабилитационные мероприятия». В обзор были включены статьи давностью не более 10 лет, относящиеся к тематике данного обзора. Отчеты о единичных наблюдениях, переписка, письма и исследования, не проводившиеся на людях, в обзор не включались.*

***Результаты:** В статье приведены данные касательно выбора наиболее эффективных технологий реабилитации больных с саркомой и приведены доводы относительно рекомендаций к внедрению в практику новых подходов и методов. Реабилитация подразделяется на несколько основных типов: медицинская (представляет собой проведение физиотерапии, применение медикаментов и др.), физическая (основана на восстановлении объёма двигательных функций, координации, силы), психологическая (включает работу над психоэмоциональным состоянием пациента), социальная (подразумевает возврат пациента к социальной активности, помощь в адаптационном периоде), реабилитация с использованием современных технологий (помощь роботизированных систем, компьютерной симуляции дополненной виртуальной реальности, использование умных часов и фитнес-браслетов).*

Индивидуально подобранные и адаптированные концепции реабилитации в рамках многопрофильной и междисциплинарной настройки имеют важное значения для оптимизации функции у пациентов с саркомой.

***Заключение:** Реабилитация пациентов с саркомой – не только медицинская, но и социальная задача. Успешное восстановление пациентов способствует их полноценному возвращению к активной жизни, что имеет большое значение для общества в целом.*

***Ключевые слова:** саркома, реабилитация, мультидисциплинарный подход, современные технологии в реабилитации.*

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USE OF COMPREHENSIVE GERIATRIC ASSESSMENT IN ONCOLOGY: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Over 60% of patients who are first diagnosed with cancer are aged 65 and older. This article analyzes the impact of Comprehensive Geriatric Assessment (CGA) on cancer treatment outcomes in elderly patients.*

The study aimed to *analyze the relationship between Comprehensive Geriatric Assessment, frailty syndrome, and cancer treatment outcomes in elderly patients.*

Methods: *An analysis of publications from the last 10 years related to the subject of this review was conducted without using language filters.*

Results: *A relationship between frailty syndrome and survival, mortality, and other outcomes in oncogeriatric patients was established. An analysis of outcome assessment measures for patients with frailty syndrome was conducted. Combinations of CGA elements applicable for the evaluation of oncogeriatric patients were highlighted.*

Conclusion: *CGA proves to be beneficial in oncogeriatric practice. It is essential to carefully select CGA elements to optimize clinical practice and solve research tasks. Further research in this field makes an important contribution to the development of oncogeriatric medicine and improving the effectiveness of cancer treatment in elderly patients.*

Keywords: *frailty syndrome, oncology, geriatrics, comprehensive geriatric assessment, intensive care.*

Introduction: According to global mortality data for 2019, more than three-quarters of the 20.4 million premature deaths among people aged 30–70 years are due to non-communicable diseases. Of every 10 people who die prematurely from non-communicable diseases, 4 die from cardiovascular diseases, and 3 die from cancer [1]. This is due to both population aging and demographic growth and increasing exposure to risk factors, key among which are tobacco, alcohol, obesity, and air pollution [2].

For example, traffic-related air pollution (TRAP) increases the risk of breast cancer and contributes to overall air carcinogenicity. However, due to the small effect size (i.e., 1.5% increase in risk for every 10 μg/m^3 increase in nitrogen dioxide (NO2) exposure) and heterogeneity across studies using surrogate variables for TRAP exposure other than NO2, the certainty of the evidence for an association between TRAP exposure and breast cancer risk remains moderate [3].

It is well known that nitric oxide (NO) plays a key role in several stages of cancer, including angiogenesis, apoptosis, cell cycle, invasion and metastasis [4].

A borderline association (odds ratio (OR) =1.4; 95% confidence interval (CI): 1.0-1.9) has been reported between breast cancer risk and childhood proximity to a road with characteristics of high exposure to traffic-related pollutants: close proximity, presence of median strip/barrier, multiple lanes, and heavy traffic [5]. Pooled estimates showed that NO_2, elemental carbon (a form of atmospheric carbon), and $PM_{2.5}$ (particles less than 2.5 micrometers in diameter) were associated with mortality from cardiovascular disease, respiratory disease, and lung cancer, with a relative risk (RR) of 1.04 (95% CI: 1.01-1.07) [6]. A meta-analysis of 14 outdoor air pollution studies in North America and Europe showed a statistically significant 9% (95% CI: 4-14%) increase in the risk of lung cancer incidence or mortality for every 10 μg/m3 increase in $PM_{2.5}$ concentration; 9 studies of PM_{10} reported an 8% (95% CI: 0-17%) increase in risk per 10 μg/m^3 [7].

A meta-analysis of seven observational studies confirmed an association between $PM_{2.5\ exposure}$ (per 10 μg/m^3 increment) and an increased risk of colorectal cancer (CRC) (OR 1.42; 95% CI: 1.12-1.79; P=0.004). Moreover, a higher Air Pollutants Exposure Score (APES) score proposed by the working group was associated with an increased risk of CRC (OR 1.03; 95% CI: 1.01-1.06; P=0.016) and worse survival (OR 1.13; 95% CI: 1.03-1.23; P=0.010), especially among participants with insufficient physical activity and ever smoking [8].

According to WHO reports, life expectancy in 2019 was 72.6 years and is expected to be 77.1 years by 2050. Older people (65 years and older) are the fastest-growing age group in the world [9]. Based on the above, the older adults (60-74 years) and senile population (75-90 years) may be potentially vulnerable to developing can-

cer, which entails the need to expand the scope of geriatric care.

Comprehensive geriatric assessment (CGA) allows for predicting the risk of severe toxic reactions to chemotherapy in older adults [10]. Based on hearing impairments identified using CGA, it is possible to predict the high toxicity of chemotherapy in elderly patients [11]. Depression, anxiety, and cognitive impairment are more common in older adults, probably due to an underestimation of their initial symptoms and inconsistent adherence to treatment [12].

Thus, selecting CGA components for assessing the functional status of oncogeriatric patients is a relevant and insufficiently studied area. This review was conducted with an emphasis on the following aspects:

– prognostic value of the CGA in common oncological diseases in the Republic of Kazakhstan (RK);

– geriatric factors influencing survival prognosis;

– CGA and assessment of therapy toxicity;

– selection of elements of the CGA for use in oncogeriatric practice;

- oncogeriatric patients in the intensive care unit (ICU).

The study aimed to analyze the relationship between Comprehensive Geriatric Assessment, frailty syndrome, and cancer treatment outcomes in elderly patients.

Objectives of the study: systematization and analysis of modern data regarding the relationship between frailty syndrome on the one hand and overall survival and mortality on the other hand in elderly cancer patients, as well as determination of CGA variants applicable in this category of patients.

Materials and methods: The articles were searched using the study keywords in the Pubmed, Web of Science, Scopus, and RINTS databases. The review included articles no older than 10 years related to the subject of this review without using language filters. The analysis included 38 articles; the relevant data were summarized as a review.

Results:

The prognosis for common oncological diseases in the Republic of Kazakhstan.

Approximately 40% of patients with CRC in developed countries are at least 75 years old [13]. The meta-analysis by S. Chen et al. (2022) included relevant cohort studies with a more than 1-year follow-up involving 35,546 patients, of whom 4,100 (11.5%) had frailty syndrome. The results showed that overall survival in patients with frailty syndrome was worse than those without frailty syndrome at baseline (OR 2.21; 95% CI: 1.43-3.41; P<0.001). Further meta-analysis with two data sets showed that frailty was also associated with worse cancer-specific survival (HR 4.60; 95% CI: 2.75–7.67; P<0.001) and recurrence-free survival (HR 1.72; 95% CI: 1.30–2.28; P<0.001) [14].

A retrospective study by S. Lee et al. (2023) examined the results of 1066 patients over 65 years of age who underwent gastric resection for gastric cancer between 2014 and 2018. All patients were divided into 2 groups: those over 80 years old – a group of elderly patients (12.8%) and those aged 65 to 79 – a group of "young" elderly people. With a median follow-up of 49.1 months, 5-year overall survival after surgery in the group of elderly patients was lower than in the group of "young" elderly (75.6% vs. 87.0%; P<0.001). However, 5-year disease-specific survival was comparable between the groups (90.1% vs. 92.2%; P=0.324). The American Society of Anesthesiologists (ASA) physical status classification, oncologic stage, and surgical tactics were independent predictors of overall survival [15].

E. Abdelfatah et al. (2023) analyzed data from 411 patients operated on for colorectal adenocarcinoma between 2011 and 2020. The mean age was 75.1 years. The mean Risk Analysis Index (RAI-A) score was 37, and 29.9% of patients had CSA. Such patients had a significantly higher rate of overall complications (30.1% vs. 14.6%; p<0.001), as well as higher rates of postoperative hospitalization for more than 30 days, the incidence of postoperative delirium, and discharge to rehabilitation. No differences in CSA were observed regarding overall, CRC-specific, or progression-free survival [16].

According to a systematic review by MR Moreno-Carmona et al. (2024), frailty syndrome in elderly patients with colon cancer is a risk factor for postoperative complications and mortality in the short (30 days), medium (3-6 months) and long-term (1 year); OR 3.67 (95% CI: 1.538.79), OR 8.73 (95% CI: 4.03-18.94) and OR 3.99 (95% CI: 2.12-7.52), respectively. Frailty syndrome also had an impact on survival with an adjusted hazard ratio (AHR) of 2.99 (95% CI: 1.70-5.2), as well as on overall and major postoperative complications with ORs of 2.34 (95% CI: 1.75-3.15) and 2.43 (95% CI: 1.72-3.43), respectively [17].

Some authors define older patients in geriatric oncology as "old" when their clinical status influences their decision-making [18]. The incidence of lung cancer increases sharply at the age of 45-49 years and peaks in the 85-89 age group for men and in the 80-84 age group for women. The average age at diagnosis in the United States is 70 years, and 68% of patients are diagnosed after age 65 [19], with challenges arising in diagnosing and treating these diseases in older adults given factors such as comorbidities, functional limitations, and difficulty taking medications [20].

The impact of frailty syndrome has also been shown for primary lung cancer. In a study of 1667 patients with primary lung cancer, 297 (17.8%) patients had frailty syndrome status according to the frailty index based on laboratory test (FI-LAB) at the time of diagnosis. The all-cause mortality rate was 61.1% (1018/1667), with a higher overall risk of death in patients with frailty syndrome, a relative risk of 1.616 (95% CI: 1.349-1.936), and a median follow-up of 650 days [21].

In a cohort study of patients with non-small cell lung cancer treated with radiotherapy, frailty syndrome was associated with lower 3-year overall survival (37.3% vs. 74.7%; p=0.003) and 3-year cumulative non-cancer death rate (36.7% vs 12.5%; p=0.02) [22].

Breast cancer remains the most common cancer in women worldwide, being the leading cause of death, while mortality rates depending on age are quite contradictory [23]. Thus, according to the reporting data of the American Cancer Society (ACS), from 2012 to 2016, the incidence rate of breast cancer increased slightly by 0.3% per year, mainly due to an increase in localization and hormone positivity. In contrast, mortality from breast cancer decreased by 40% from 1989 to 2017, with a decline rate of 1.3-1.9% [24].

The results of a French study including patients over 70 years of age with breast cancer showed that age remains a risk factor for heterogeneity in oncological practice, which requires the disclosure of specific recommendations, with geriatric covariates being the main components in the decision-making process [25].

S. Wang et al. (2022) examined 4645 publications on the prevalence of frailty syndrome among patients with breast cancer: the meta-analysis included data from 24 studies involving 13510 people. The prevalence of frailty syndrome among patients with breast cancer in individual studies ranged from 5 to 71%. The prevalence of frailty syndrome was 43% (95% CI: 36-50%; p<0.05). Subgroup analysis showed that the therapeutic method, frailty syndrome scales, age, regions, years of publication, and study quality were associated with the prevalence of frailty syndrome among patients with breast cancer and that frailty syndrome may also be characteristic of "younger" age patients and has prognostic value [26].

A retrospective cohort study by CH Yan et al. (2021) of patients with breast cancer aged ≥65 years assessed the association between pre-diagnosis frailty syndrome and the risk of breast cancer-specific and all-cause mortality in older women. Fewer women with frailty syndrome than "robust" women underwent breast-conserving surgery (52.8% vs. 61.5%) and radiation therapy (43.5% vs. 51.8%). In a multivariate analysis of the study data, the degree of asthenia was not associated with breast cancer-specific mortality (patients with frailty syndrome vs. robust patients, Relative OR 1.47; 95% CI: 0.97-2.24). However, women with BC and frailty syndrome had a higher risk of all-cause mortality than "strong" women with BC (OR 2.32, 95% CI: 1.84-2.92) [27].

Geriatric factors influencing survival prognosis.

In a prospective analysis from 2003 to 2012, JX Moore et al. (2020) examined the impact of frailty syndrome on the association between cancer survival and sepsis incidence: cancer survivors had a more than 2-fold increased risk of sepsis, and frailty syndrome rates accounted for less than 1% of this difference [28].

JC Brown et al. (2015) assessed the associations between pre-asthenia, asthenia, and mortality among 416 older adult cancer survivors (mean age 72.2 years). Mortality varied by degree of asthenia, with a median survival of 13.9 years among "robust" survivors (53.6% of total), 9.5 years among pre-asthenic (37.3% of total), and 2.5 years among survivors with frailty syndrome (9.1% of total). Preasthenia and frailty syndrome increase the risk of premature mortality in older adults who have survived cancer [29].

In the study by Bensken WP et al. (2022) for the period from 2012 to 2016, the association between mortality and primary breast cancer, colorectal cancer, lung cancer, or prostate cancer was examined in older people (n=29140). Patients with lung cancer had the highest levels of multiple comorbid conditions, multimorbidity, and frailty syndrome. After adjustment for age, sex (only for colorectal and lung cancer), and stage, a positive association was found between all these indicators and a higher risk of death. In breast cancer patients with 5 or more comorbidities, the ROR was 1.63 (95% CI: 1.38-1.93), and in those with moderate asthenia, the ROR was 3.38 (95% CI: 2.12–5.41), with the prognosis for lung cancer being worse than for breast, prostate, or CRC cancer [30].

Comorbidities measured by the Charlson Comorbidity Index (p=0.001) and Lawton-Brodie score (p=0.011); anastomotic failure (p=0.024); lymph node involvement (p=0.005); distant metastasis (p<0.001); high TNM stage (p=0.004) and anastomotic defect (p=0.013) were significant predictors of poor prognosis. Multivariate analysis of long-term survival, adjusting for age, asthenia, comorbidities, and TNM stage, showed that comorbidities (RH 1.30; 95% CI: 1.10-1.54) and TNM stage (RH 2.06; 95% CI: 1.16-3.67) were the only independent risk factors for survival at 5 years. Frailty syndrome is associated with poor short-term postoperative outcomes but does not affect long-term survival in elderly patients with colorectal cancer. In turn, comorbidities and tumor stage are predictors of long-term survival [31].

In a prospective study, E. Boutin et al. (2018) assessed the association between obesity and adverse events in older women, depending on their frailty syndrome status. The risk of death over 5 years of follow-up among asthenic women (frailty syndrome determined by the Fried method), compared with "non-frail" women with normal weight, decreased with increasing body mass index (BMI) after adjusting for age, cardiovascular drugs, hospitalization in the last 12 months, and functional status [32].

Some authors describe the "survival paradox of obese cancer patients": this study included 433 patients with a mean age of 81.2±6.0 years; 51% were women. Of all patients, 44.3% had gastrointestinal cancer, 18% had breast cancer, 14.5% had lung cancer, and 45% had metastases, while 20.3% had obesity at outcome. Obesity was independently and inversely associated with 6-month mor-

tality only in patients with metastatic lesions (Relative Risk Factor 0.17; 95% CI: 0.03–0.92) [33].

CGA and assessment of therapy toxicity.

Numerous studies have shown that adherence rates to oral chemotherapy among cancer patients range from 46% to 100% in the general population and depend on age, patient sample, drug type, follow-up period, and adherence assessment and calculation measure [7, 30, 34]. In older adults, non-adherence is facilitated by various factors. Sleep disturbances (40%) and cognitive impairment, which are present in approximately 25-47% of older cancer patients, and hearing loss in 25% of older cancer patients, contribute to the problem [35]. Older patients often have difficulty with transportation, leading to missed appointments or non-compliance with prescriptions [36].

In the study by A. Hurria et al. (2016), factors influencing chemotherapy toxicity were studied, a model was formed, and a toxicity scale was proposed. The average age of the study sample (n=250) was 73 years (from 65 to 94 years, standard deviation 5.8). The risk of toxicity increased with an increase in the risk index (36.7% – low, 62.4% – medium, 70.2% – high risk; P<0.001), while it was noted that there was no relationship between the Karnofsky index and chemotherapy toxicity (P=0.25) and the index did not work [10].

This scale allows for determining the risk of developing toxicity of stages 3–5 according to the classification of common terminology criteria for adverse events (CTCAE) [37] and determining which group of patients requires greater monitoring for adverse events.

Selection of elements of the CGA for use in oncogeriatric practice.

The choice of a set of tests for conducting the CGA in the context of practice and solving research problems also represents a challenge for physicians and researchers [38]. The frequency of frailty syndrome ranged from 23 to 97%, depending on the number of included CGA domains. J. Kenig et al. (2015) identified the CGA components that had prognostic value in a small sample of patients [39]:

1. Activities of Daily Living (ADL);
2. Instrumental Activities of Daily Living (IADL);
3. The Blessed Orientation-Memory-Concentration Test (BOMC);
4. The Clock Drawing Test (CDT-test);
5. The Folstein Mini-Mental State Examination (MMSE);
6. The Charlson Comorbidity Scale (CCS);
7. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G);
8. The Geriatric Depression Scale (GDS);
9. The Timed Up and Go (TUG);
10. The Mini Nutritional Assessment (MNA);
11 Eastern Cooperative Oncology Group performance status (ECOG-PS);
12. Preoperative assessment of physical status according to ASA.

The authors identified the following combinations of tests that had prognostic value: (1) Basic set + MNA + TUG + CCS + polypharmacy (>4 or >5 drugs/day); (2) Basic set + MNA + TUG + CCS + polypharmacy (>4 or >5 drugs/day) + SSS, (3) Basic set + MNA + TUG + CIRS-G + polypharmacy (>5 drugs/day), (4) Basic set + MNA + TUG + CIRS-G + polypharmacy (>4 or >5 drugs/day) + SSS, (5) PACE (with Satariano index 2+).

The core set included ADL/IADL, GDS-15, and BOMC/CDT following the definition formulated by the International Society of Geriatric Oncology (SIOG), which states that at least the CGA for older patients with cancer should include assessment of functional status, mood, and cognitive function.

Overall, these CGA test sets are consistent with the studies described above that used these clinical tests and scales despite the heterogeneity in the choice of method for determining CSA.

Oncogeriatric patients in ICU settings.

A multicentre retrospective cohort study of adult patients admitted to the ICU between 2018 and 2022 (158 Australian ICUs, aged ≥16 years) examined the association between frailty syndrome and survival time after elective cancer surgery. For elective surgical patients, frailty syndrome was associated with lower survival (RHR 1.72, 95% CI: 1.59-1.86) and mortality at baseline up to 10 months of follow-up (RHR 1.39; 95% CI: 1.03-1.86), but this association then plateaued, and its predictive power further diminished over time up to 4 years (RHR 1.96; 95% CI: 0.73-5.28). Frailty syndrome has been associated with worse outcomes following ICU admission after elective cancer surgery, particularly in the short term [40].

For patients admitted to the ICU (166 Australian ICUs; age ≥16 years) with metastatic cancer in the study by Alamgeer et al. (2023), overall survival at 4 years was lower in asthenic patients compared with "robust" patients (29.5% vs. 10.9%; p<0.0001). Frailty syndrome was associated with shorter 4-year survival (adjusted Relative Risk 1.52; 95% CI: 1.43-1.60), and this effect was observed across all cancer subtypes. Frailty syndrome was associated with shorter survival times in patients aged <65 years (RHR 1.66; 95% CI: 1.51-1.83) and aged ≥65 years (RHR 1.40; 95% CI: 1.38-1.56), but its effect was stronger in patients aged <65 years (p<0.0001). Thus, in patients with metastatic cancer admitted to the ICU, frailty syndrome was associated with worse long-term survival [41].

A. Subramaniam et al. (2022) in their multicenter study (16 ICUs; 7001 patients; mean age 63.7 (49.1-74.0) years; mean APACHE II score – 14; 3266 patients (46.7%) were on mechanical ventilation; hospital mortality – 9.5% (n=642); annual mortality – 14.4%) compared the results of the Clinical Frailty Scales (GFS) and the Hospital Frailty Risk Score (HFRS) in critically ill patients to predict long-term survival up to one year after ICU admission. The result was that both scales have prognostic value in assess-

ing survival up to 1 year after admission to the ICU, but the GFS scale was still a better predictor of 1-year survival than the HFRS [42].

There is no doubt that traditional preoperative examination is insufficient for older adults. Therefore, widespread implementation of a comprehensive assessment of the initial geriatric status [43], particularly in cancer patients, will improve approaches to making surgical decisions and help develop optimal anesthetic safety strategies [44]. Thus, according to S. Sigaut et al. (2021), the Confusion Assessment Method (CAM) in the surgical department and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) are proposed for assessing postoperative delirium among operated patients aged 70 years and older [45]. The following clinical tests are recommended as part of the CGA to ensure the management of surgical patients with an oncogeriatric profile [45-47]:

1. CAM-ICU;

2. Checklist For screening delirium V ICU (Intensive Care Delirium Screening Checklist, ICDSC).

In studies requiring an assessment of the impact of CGA on patients' hospital stay, the following endpoints related to patients' stay in the ICU are proposed [48-50]:

1. hours spent on artificial ventilation;

2. duration of hospitalization;

3. presence of perioperative complications;

4. cost of inpatient treatment.

It is also worth noting that the Clavien-Dindo classification of morbidity/surgical complications [51] is widely used to assess outcomes in oncogeriatric patients admitted to the ICU.

Discussion: Key data from meta-analyses and systematic reviews over the last ten years are considered, which show that the use of CGA can improve the prognosis and quality of life of elderly patients with cancer. It was also revealed that age, comorbidities, asthenia, and other geriatric aspects are associated with worsening survival and increasing mortality among cancer patients. An analysis of outcome measures in patients with frailty syndrome was conducted. Combinations of CGA elements that are applicable for assessing oncogeriatric patients are identified.

Research highlights the need to incorporate geriatric aspects into oncology practice to improve the prognosis of treatment outcomes in elderly patients. This approach ensures therapy personalization, considering each patient's health characteristics and needs.

Conclusion: This article examines the relationship between CGA and cancer treatment outcomes. Current methods of CGA application in oncogeriatrics are discussed. This identifies future research directions in oncogeriatrics and highlights the impact of CGA on ICU patient management.

Continuing research in this area is important for developing oncogeriatric medicine and improving the effectiveness of treating elderly patients with cancer. Particular attention should be paid to integrating the obtained data into clinical practice to optimize the care of cancer patients in intensive care settings.

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АҢДАТПА

ОНКОЛОГИЯДА КЕШЕНДІ ГЕРИАТРИЯЛЫҚ БАҒАЛАУДЫ ҚОЛДАНУ: ӘДЕБИЕТТЕРГЕ ШОЛУ

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Өзектілігі: *Қатерлі ісікке жаңадан шалдыққан науқастардың 60%-дан астамы 65 жастан асқандар. Бұл мақалада егде жастағы емделушілерде жан-жақты кешенді гериатриялық бағалаудың (кейін КГБ) онкологиялық ауруларды емдеу нәтижелеріне әсерін талдау ұсынылады.*

Зерттеу мақсаты *– КГБ, қарттық астения синдромы (кейін ҚАС) және егде жастағы науқастардағы қатерлі ісіктерді емдеу нәтижелері арасындағы байланысты талдау.*

Әдістері: *Соңғы 10 жылдағы осы шолу тақырыбына қатысты жарияланымдарға талдау тілдік сүзгілерді қолданбай жүргізілді.*

Нәтижелері: *Онкогериатриялық науқастарда ҚАС көрсеткіштері мен өмір сүру, өлім және басқа нәтижелер арасындағы байланыс анықталды. ҚАС бар науқастарда нәтиже шараларына талдау жасалды. Онкогериатриялық науқастарды бағалау үшін қолданылатын КГБ элементтерінің комбинациясы анықталды.*

Қорытынды: *КГБ онкогериатриялық тәжірибеде пайдасын көрсетеді. Клиникалық тәжірибені оңтайландыру және зерттеу мәселелерін шешу үшін КГБ элементтерін таңдауда мұқият болу керек. Бұл саладағы алдағы зерттеулер онкогериатриялық медицинаның дамуына және егде жастағы онкологиялық науқастарды емдеудің тиімділігін арттыруға маңызды үлес болып табылады.*

Түйінді сөздер: *қарттық астения синдромы, онкология, гериатрия, кешенді гериатриялық бағалау, қарқынды терапия.*

АННОТАЦИЯ

ИСПОЛЬЗОВАНИЕ КОМПЛЕКСНОЙ ГЕРИАТРИЧЕСКОЙ ОЦЕНКИ В ОНКОЛОГИИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Более 60% пациентов, у которых впервые диагностировано онкозаболевание, находятся в возрасте 65 лет и старше. Данная статья представляет анализ влияния комплексной гериатрической оценки (КГО) на результаты лечения онкологических заболеваний у пожилых пациентов.*

Цель исследования *– анализ взаимосвязи между КГО, синдромом старческой астении (ССА) и результатами лечения онкологических заболеваний у пожилых пациентов.*

Методы: *Был проведен анализ публикаций за последние 10 лет, относящихся к тематике данного обзора, без применения фильтров по языку.*

Результаты: *Выявлена связь между показателями ССА и выживаемостью, смертностью и иными исходами у онкогериатрических пациентов. Проведен анализ мер оценок исходов у пациентов с ССА. Выделены комбинации элементов КГО, которые применимы для оценки онкогериатрических пациентов.*

Заключение: *КГО демонстрирует пользу в онкогериатрической практике. Необходимо тщательно подходить к отбору элементов КГО для оптимизации клинической практики и решения исследовательских задач. Дальнейшие исследования в этой области представляют важный вклад в развитие онкогериатрической медицины и повышение эффективности лечения пациентов с раком в пожилом возрасте.*

Ключевые слова: *синдром старческой астении (ССА), онкология, гериатрия, комплексная гериатрическая оценка (КГО), интенсивная терапия.*

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FACTORS AFFECTING THE SELF-EFFICACY OF HEALTHCARE MANAGERS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *This review analyses the literature on the factors influencing the self-efficacy of healthcare managers. In modern medical practice and healthcare management, managers must address complex tasks related to the organization of healthcare institutions, efficient resource allocation, and providing high-quality patient care. The psychological phenomenon known as self-efficacy is an essential factor in accomplishing these tasks. This refers to the ability of managers to recognize their capabilities and apply them to achieve goals in their professional activities. Although many managers can set and strive to achieve goals, many face difficulties. Therefore, studying the factors affecting the self-efficacy of healthcare managers is critical for improving management in the healthcare system and enhancing its effectiveness.*

The study aimed to *review the factors that influence the self-efficacy of healthcare managers to identify key aspects that affect performance and management quality in healthcare institutions.*

Methods: *The research reviewed existing scientific works focused on studying the factors influencing the self-efficacy of healthcare managers.*

Results: *During the analysis, particular attention was given to methods for assessing professional confidence, leadership qualities, and stress resilience of managers, as well as identifying factors affecting their ability to make effective managerial decisions in the real-world context of healthcare practice. Data extraction revealed various performance indicators, key findings, and recommendations.*

Conclusion: *The career growth and personal development of healthcare workers, which are actively studied in foreign psychology, are increasingly relevant for Kazakhstani specialists in light of the changing requirements and challenges in healthcare. Studying the self-perception and self-awareness of individuals who have succeeded in their medical careers is of great importance both from a theoretical and practical perspective, as it helps improve professional skills and the overall approach to providing medical care within the dynamically changing healthcare system.*

Keywords: *self-efficacy, manager, health care, psychology.*

Introduction: In modern medical practice and healthcare management, managers must address complex tasks related to the diagnosis, treatment, and prevention of diseases, as well as maintain effective communication with patients. The psychological phenomenon known as self-efficacy is an essential factor in accomplishing these tasks. This refers to the ability of managers to recognize their capabilities and apply them to achieve goals in their professional activities. Although many managers can set and strive to achieve goals, many face difficulties. Therefore, studying the factors affecting the self-efficacy of healthcare managers is critical for improving management in the healthcare system and enhancing its effectiveness.

Self-efficacy is a key element of healthcare workers' professional development that significantly impacts their professional activities. In recent years, research in this area has been linked to transformations in the socio-economic and organizational spheres, which directly affect healthcare workers' professional activities. The career growth and personal development of healthcare workers, which are actively studied in foreign psychology, are increasingly relevant for Kazakhstani specialists in light of the changing requirements and challenges in healthcare. Studying the self-perception and self-awareness of individuals who have succeeded in their medical careers is of great importance both from a theoretical and practical perspective, as it helps improve professional skills and the overall approach to providing medical care within the dynamically changing healthcare system.

The study aimed to review the factors that influence the self-efficacy of healthcare managers to identify key aspects that affect performance and management quality in healthcare institutions.

Materials and Methods: The study reviewed existing scientific works focused on studying the factors influencing the self-efficacy of healthcare managers. The review included articles, monographs, dissertations, and other publications covering psychological aspects, leadership qualities, and stress resistance of managers, as well as methods for assessing their profession-

al confidence and ability to make managerial decisions in healthcare.

The literature search process included:

– *Key databases:* The analysis was conducted based on publications available in international scientific databases such as PubMed, Scopus, and Google Scholar, as well as in psychology and healthcare journals.

– *Inclusion criteria:* Articles were selected that explored theoretical and empirical aspects of self-efficacy in healthcare, emphasizing factors influencing the successful performance of management tasks in medical institutions.

– *Keywords:* The following keywords were used for the search: "self-efficacy," "health care management," "health psychology," "professional confidence," "leadership qualities in health care," and "stress resistance of managers."

– *Methods of analysis:* Data analysis, content analysis, and synthesis of existing studies allowed for identifying main trends and factors affecting the self-efficacy of healthcare workers. The leadership skills, professional confidence, and stress on managerial activity in medical institutions were underlined in this study.

– *Assessment of study quality:* The quality and relevance of the studies included in the review were assessed, considering the methodological approaches and representativeness of the samples described in the relevant works.

Thus, this study is based on an extensive analysis of existing scientific publications, which allowed us to comprehensively examine the self-efficacy factors of healthcare managers and their impact on the effectiveness of management in medical institutions.

Results: The concept of self-efficacy was first introduced by the American psychologist A. Bandura in the 1970s of the 20th century. This phenomenon was defined as a specific type of cognitive thinking that regulates the goal-oriented activity of an individual through cognitive, motivational, affective, and physiological processes [1]. Subsequent studies have established that self-efficacy should be considered as a manifestation of confidence [2], faith [3], and ability [4] of a person who determines their ability to realize or not to realize expected results in the process of completing tasks and interacting with others.

Scientists identify several key aspects that contribute to the replenishment of self-efficacy:

1. The ability to learn contributes to accumulating personal experience of the subject.

2. Emotional stability, characterized by a low level *of anxiety*.

3. Emotional processes that have different effects on self-efficacy. In the case of a positive orientation of the subject, there is an increase in inspiration and desire for productive activity. On the contrary, with a negative orientation, anxiety, constraint, fear, and inhibition increase.

4. Significant people's *social support*, particularly in the form of approval, helps to strengthen the positive experience of self-efficacy [5]. Social support is most effective if it comes from a significant individual, is timely, and meets expectations. Various circumstances can strengthen the belief in self-efficacy as the ability to control life events. Personal experience, both positive and negative, predetermines not only life expectations but also professional expectations that arise in the context of activities and communication.

Self-efficacy is a cognitive dispositional resource that promotes adaptation and an individual's psychological well-being [6].

Improving quality and increasing safety within national healthcare systems is a priority for many countries. This is confirmed by the results of scientific research and the activities of international organizations, as well as strategic priorities outlined in state policies in public health [7].

Studies have shown that self-efficacy influences attitudes toward work, professional training, job satisfaction, educational level, and susceptibility to new knowledge [8]. Thus, self-efficacy is considered one of the key factors determining the degree of effort and resources a person is ready to mobilize to solve emerging problems. It helps to increase the energy level, ensures its targeted use, and stimulates stability in achieving goals [9]. Some researchers [10-12] confirm that high self-efficacy is a key element of initiative and self-confidence necessary to achieve goals.

Thus, to successfully perform their duties and solve problems in the healthcare sector, managers must rely on accumulated experience, professional knowledge, and analytical skills. With an increase in the volume of knowledge and improvement of management skills, they become more prepared to develop effective and comprehensive solutions to improve the quality of medical services and increase the efficiency of medical institutions.

A high level of education and specialized training of healthcare managers contributes to developing their professional competencies and confidence in decision-making. Research conducted in Kazakhstan shows that a lack of proper training can significantly reduce the self-efficacy of medical psychologists, negatively affecting their ability to effectively perform professional duties. The ability of managers to cope with stress and maintain psychological stability in difficult situations directly affects their self-efficacy. According to research, low levels of self-efficacy in the emotional sphere are associated with depression, anxiety, and a sense of help-

lessness [13]. In human-to-human interaction (including health workers, psychologists, and teachers), it is impossible to completely avoid stressful situations [14].

Comparative Analysis of Self-Efficacy Factors of Healthcare Managers: International Experience and Kazakhstan

An analysis of factors influencing the self-efficacy of healthcare managers revealed both general trends and specific differences between international practice and the situation in Kazakhstan.

International experience (2015-2025) and the situation in Kazakhstan:

Psychological confidence and leadership skills: Managers with high self-efficacy confidently make decisions and motivate teams, which contributes to improving the quality of medical services. Cross-cultural studies show that psychological confidence and leadership skills depend on factors such as country of residence, age, and professional experience of health workers [15-17].

Stress resistance and adaptation to change: The ability to cope with stress and adapt to changes is critical in the dynamic development of healthcare. World practice emphasizes the importance of these skills for effective management in crises [18-19]. Given the specific working conditions in medical institutions, issues of stress resistance are relevant. However, these issues have not been fully studied and researched in Kazakhstan.

Professional skills and experience: Extensive experience and developed professional skills enable managers to effectively solve complex problems and implement innovations [20]. In Kazakhstan, they also tend to improve professional skills, which is reflected in the contents of secondary education [21].

Training and development: Continuous training and development of new management methods contribute to improving managers' self-efficacy. World practice confirms that systematic professional development is key to success in healthcare management [22]. Continuous training and implementation of new management methods contribute to improving managers' self-efficacy. However, additional research is required to assess the availability and quality of such programs in Kazakhstan.

Organizational Culture and Support: A strong organizational culture that supports innovation and collaboration helps to increase managers' confidence. In Kazakhstan, issues of preserving and developing cultural values also affect performance in various areas, including healthcare [23-26]. The implementation of employee support programs and the development of a positive organizational culture help to increase manager self-efficacy. However, the extent to which these initiatives are implemented in Kazakhstan remains understudied.

Discussion: Healthcare workers must have extensive knowledge and practical skills to perform their duties effectively, as in other areas. In recent years, the education system for healthcare workers in Kazakhstan has undergone significant changes to meet international standards and best global practices. Key training areas include healthcare, strategic planning, medical law and ethics, and personnel and resource management. However, the study shows that educational programs in Kazakhstan still require further improvement to meet modern challenges, such as the digitalization of healthcare and the introduction of innovative technologies. Particular attention should be paid to developing management skills in crises, such as the COVID-19 pandemic, which requires updating educational approaches. The lack of regular updates in training and insufficient attention to the practical aspects of management continue to be important challenges for the Kazakhstan healthcare system.

Conclusion: Improving the performance of healthcare workers requires systematic improvement of personnel policy, implementation of continuous professional training programs, and active use of modern technologies in Kazakhstan. An important aspect is also maintaining specialists' emotional stability and stress resistance. Ultimately, increasing the level of self-efficacy of healthcare managers leads to improved quality of medical services, strengthening patient trust, and ensuring long-term sustainability and development of healthcare institutions.

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АҢДАТПА

ДЕНСАУЛЫҚ САҚТАУ САЛАСЫНДАҒЫ МЕНЕДЖЕРЛЕР: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Бұл зерттеу денсаулық сақтау саласындағы менеджерлердің өз-өзіне сенімділік факторларын талдауға арналған әдебиеттердің шолуын ұсынады. Қазіргі медициналық практика мен денсаулық сақтау саласын басқаруда менеджерлерден медициналық ұйымдардың жұмысын ұйымдастыру, ресурстарды тиімді бөлу және пациенттерге сапалы қызмет көрсету сияқты күрделі міндеттерді шешу талап етіледі. Бұл міндеттерді сәтті жүзеге асырудағы маңызды фактор – өзін-өзі сенімділік деп аталатын психологиялық құбылыс. Менеджерлердің өз мүмкіндіктерін түсініп, оларды кәсіби мақсаттарға жету үшін пайдалану қабілеті олардың кәсіби қызметіндегі маңызды аспект болып табылады. Алайда, көптеген менеджерлер мақсаттар қоюға қабілетті болса да, оларды іске асыруда қиындықтарға тап болады. Сондықтан денсаулық сақтау саласындағы менеджерлердің өз-өзіне сенімділігіне әсер ететін факторларды зерттеу денсаулық сақтау жүйесінде басқаруды жетілдіру және оның тиімділігін арттыру үшін маңызды міндет болып табылады.*

Зерттеу мақсаты *– денсаулық сақтау мекемелеріндегі менеджменттің өнімділігі мен сапасына әсер ететін негізгі аспектілерді анықтау үшін денсаулық сақтау саласындағы менеджерлердің өзіндік тиімділік факторлары туралы жарияланымдарға жүйелі шолу жасау болып табылады.*

Әдістері: *Зерттеу барысында денсаулық сақтау саласындағы менеджерлердің өз-өзіне сенімділігіне әсер ететін факторларды зерттеуге арналған ғылыми жұмыстардың талдауы жүргізілді.*

Нәтижелері: *Талдау барысында кәсіби сенімділік, көшбасшылық қасиеттер мен стреске төзімділікті бағалау әдістеріне, сондай-ақ олардың денсаулық сақтау саласында нақты жағдайда тиімді басқарушылық шешімдер қабылдау қабілетіне әсер ететін факторларға ерекше назар аударылды. Деректерді талдау әртүрлі нәтижелілік көрсеткіштерін, негізгі қорытындыларды және ұсыныстарды айқындады.*

Қорытынды: *Шетел психологиясында белсенді зерттеліп келе жатқан медициналық қызметкерлердің мансаптық өсуі мен тұлғалық даму мәселелері Қазақстандық мамандар үшін денсаулық сақтау саласындағы талаптар мен сын-қатерлердің өзгеруі жағдайында барған сайын өзекті болуда. Өз мансабында табысқа жеткен тұлғалардың өзін-өзі сезінуі мен өзін-өзі тануы мәселесін зерттеу теориялық және практикалық тұрғыдан маңызды, себебі бұл кәсіби дағдыларды ғана емес, сондай-ақ өзгермелі денсаулық сақтау жүйесінде медициналық көмек көрсетуге деген жалпы көзқарасты жақсартуға ықпал етеді.*

Түйінді сөздер: *өзіндік тиімділік, менеджер, денсаулық сақтау, психология.*

АННОТАЦИЯ

ФАКТОРЫ САМОЭФФЕКТИВНОСТИ МЕНЕДЖЕРОВ В ЗДРАВООХРАНЕНИИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Данный обзор представляет собой анализ литературных данных о факторах самоэффективности менеджеров в здравоохранении. В условиях современной медицинской практики и управления в здравоохранении к менеджерам предъявляются высокие требования по решению сложных задач, связанных с организацией работы медицинских учреждений, эффективным распределением ресурсов и обеспечением качественного обслуживания пациентов. Важнейшим фактором успешного выполнения этих задач является психологическое явление, известное как самоэффективность. Это способность менеджеров осознавать свои возможности и применять их для достижения целей в профессиональной деятельности. Несмотря на то что многие менеджеры способны ставить перед собой цели и стремиться к их реализации, значительная часть сталкивается с трудностями при их достижении. Поэтому изучение факторов, влияющих на самоэффективность менеджеров в здравоохранении, представляет собой актуальную задачу для улучшения управления в системе здравоохранения и повышения ее эффективности.*

Цель исследования *– провести систематический обзор публикаций о факторах самоэффективности менеджеров в здравоохранении для выявления ключевых аспектов, влияющих на производительность и качество управления в медицинских учреждениях.*

Методы: *в рамках исследования был проведен обзор существующих научных работ, направленных на изучение факторов самоэффективности менеджеров в здравоохранении.*

Результаты: *В процессе анализа особое внимание было уделено методам оценки профессиональной уверенности, лидерских качеств и стрессоустойчивости менеджеров, а также выявлению факторов, влияющих на их способность принимать эффективные управленческие решения в условиях реальной практики здравоохранения. Извлечение данных показало различные показатели результативности, ключевые выводы и рекомендации.*

Заключение: *проблемы карьерного роста и становления личности медицинских работников, активно исследуемые в зарубежной психологии, становятся все более актуальными и для Казахстанских специалистов в условиях изменений требований и вызовов в здравоохранении. Изучение самоощущения и самосознания людей, которые достигли успеха в своей медицинской карьере, имеет важное значение как с теоретической, так и с практической точек зрения, позволяя улучшить не только профессиональные навыки, но и общий подход к оказанию медицинской помощи в условиях динамично меняющейся системы здравоохранения.*

Ключевые слова: *самоэффективность, менеджер, здравоохранение, психология.*

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PROGNOSTIC VALUE OF URINARY TISSUE INHIBITOR OF METALLOPROTEINASE-2 (TIMP-2) AND INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7 (IGFBP-7) FOR CONTRAST-INDUCED ACUTE KIDNEY INJURY: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Contrast-induced acute kidney injury (CI-AKI) is a serious complication of medical procedures using contrast agents. Despite the decrease in the incidence of acute kidney injury (AKI), CI-AKI remains one of the leading causes of renal function deterioration, especially in emergencies. Serum creatinine (SCr) is not a reliable biomarker for early diagnosis since its level increases only when more than 50% of renal mass is lost. Modern iodinated contrast agents (ICA) reduce the risk of AKI but remain dangerous for patients with chronic kidney disease (CKD) and diabetes.*

The study aimed to *summarize published studies of TIMP-2 and IGFBP-7 early biomarkers to improve the diagnosis and prognosis of contrast-induced acute kidney injury.*

Methods: *The sources were searched in Pubmed, Web of Science, and Cochrane databases. The review included 21 sources published from 2014 to 2025.*

Results: *Iodized contrasts are widely used in clinical procedures. They increase the risk of CI-AKI, with intensive therapy remaining the only supportive measure. [TIMP-2]·[IGFBP7] biomarkers predict the development of severe AKI (KDIGO stage 2/3), mortality, and AKI severity with high sensitivity and accuracy. Elevated levels of these biomarkers are associated with the risk of death or dialysis within 9 months, making them useful for close patient monitoring.*

Conclusion: *Recent studies have highlighted the importance of early diagnosis of CI-AKI using IGFBP-7 and TIMP-2 biomarkers, which is important for early intervention and improved treatment outcomes. Further studies will help improve the understanding and management of this complication, considering risk factors such as creatinine levels, diabetes, and heart failure. The need for safe and effective methods for diagnosing and preventing CI-AKI is relevant both in Kazakhstan and abroad. Careful monitoring of high-risk patients and tailoring AKI management to individual patient needs can improve clinical practice and reduce the incidence of end-stage kidney failure.*

Keywords: *urinary tissue metalloproteinase-2 inhibitor (TIMP-2), insulin-like growth factor 7 binding protein (IGFBP7), contrast-induced acute kidney injury (CI-AKI), biomarkers.*

Introduction: Serum creatinine (SCr) is unreliable for detecting changes in renal function since its increase becomes noticeable only when more than 50% of the renal mass is lost. It delays the diagnostics of acute renal failure (ARF) and complicates corrective interventions. Therefore, early biomarkers of contrast-induced acute kidney injury (CI-AKI) are important for prognosis improvement. CI-AKI is defined as an absolute (0.5 mg/dL, 44 μmol/L) or relative (25%) increase in SCr in 48-72 hours after exposure to contrast medium [1].

Typically, the contrast medium causes rapid non-physiological vasodilation followed by prolonged vasoconstriction, rapidly decreasing renal blood flow. Further, this process results in a vicious cycle of medullary ischemia, which, in turn, causes the generation of reactive oxygen species and, therefore, damage to the endothelium and tubules of the vessels. The direct effects of kidney damage from contrast exposure are due to the toxicity of the tubular epithelium, confirmed by the violation of cell integrity, which leads to loss of function, apoptosis, and, ultimately, necrosis. The contrast dye also increases blood viscosity, reduces microcirculation, and lowers urine flow rate. It increases the time CM stays in the body and can cause microvascular thrombosis. All this results in a sharp decrease in the glomerular filtration rate (GFR) and kidney function. In 2012, 33,249 hospitalizations for acute myocardial infarction were reported in 31,532 patients in the United States and showed that the incidence of ARF decreased from 26.6% in 2000 to 19.7% in 2008 (a decrease of 26%). Although the incidence of CI-AKI may have historically declined over the past decade, the risk is still significant in patients with the greatest need for urgent percutaneous coronary intervention, including patients with ST-elevation myocardial infarction and patients with cardiogenic shock [2].

In hospitals, CI-AKI is one of the most common iatrogenic causes of ARF. As a result of the development of

diagnostic and interventional imaging methods, contrast-induced renal injury was the third leading cause of iatrogenia in hospitalized patients undergoing diagnostic and interventional procedures in Greece, Germany, and the United States in the 2010s [1]. Mild forms of acute kidney injury (AKI) are associated with high mortality and morbidity. The toxicity of iodinated contrast media (ICM) is an important cause of ARF in the intensive care unit (ICU). Modern ICMs with low osmolarity are less likely to cause ARF than older drugs. Over the past 40 years, the osmolality of available contrast agents has gradually declined to physiological levels. Only high-osmolar products (e.g., diatrizoate) with 5 to 8 times higher osmolality than plasma were used in the 1950s. Red blood cell deformity, systemic vasodilation, intrarenal vasoconstriction, and direct toxicity of the renal tubules are more common with contrast agents with osmolality greater than that of blood. This is confirmed in a meta-analysis of studies up to 1992 [3]. ICMs are water-soluble benzene rings in the form of monomers or dimers. Modern ICMs for intravascular injections are iso-osmolar iodixanol and low-osmolar non-ionic monomers. Highly osmolar ICMs are no longer used. The viscosity of iodixanol (11.8 cPs) is significantly higher than that of yohexol (6.3 cPs), the lowest in the category with a low osmolar content. Urine viscosity may be significantly higher with iodixanol in an experimental rat model. Temporary dilation may be followed by a period of sustained vasoconstriction that lasts several hours in the renal arcade of blood vessels subdivided into afferent glomerular arteriole serving the glomerulus, efferent arteriole dividing and forming a peritubular network. As a result, contrast stasis is observed in the kidneys after the completion of the procedure. The uptake of ICM by cells leads to cell swelling and apoptosis [4].

According to the neutrophil gelatinase-associated lipocalin (NGAL) assay results, a subclinical CI-AKI microembolism not found clinically may explain part of CI-AKI since the kidneys receive 25% of cardiac output. Direct complications include volume overload, hyperkalemia, end-stage chronic renal failure, and death. Patients with CI-AKI have a higher risk of myocardial infarction, bleeding, and mortality [4].

To date, there are no effective pharmaceuticals for the prevention or treatment of CI-AKI. Diagnostic procedures using ICM are often denied for patients with chronic kidney disease (CKD). Early detection of ARF is difficult, as it is diagnosed only with an increase in SCr or a decrease in diuresis [3].

ICMs are widely used for diagnostics and surgical treatment but cause iatrogenic renal dysfunction. With a decrease in renal parenchyma mass and fewer nephrons in patients with CKD and diabetes, the decrease in renal blood flow can be quite persistent. It impairs oxygenation of the external medulla and leads to ischemia of the proximal and distal tubules. Besides, water-soluble contrast is readily absorbed by the apical surface of the proximal tubular cells and from the basal-lateral surface into the tubulointerstitial space. Tubular cells undergo swelling and apoptosis.

Attempts to make iodine-based radiographic contrast medium less toxic are promising, especially with cyclodextrin, which retains contrast in the urinary space and reduces the likelihood of its penetration into kidney tissue and kidney damage. Today, significant funds in invasive cardiology have been invested in fluoroscopy and cineangiography for many years [4].

In severe cases, CI-AKI causes progressive oliguria requiring dialysis associated with high mortality. This is about 10% of all cases of iatrogenic kidney disease. Although the incidence is low (1-6%), this rate is high in at-risk groups. Therefore, early identification of high-risk patients is important to improve treatment outcomes [5]. In Kazakhstan, NGAL testing is still conducted only by commercial laboratories according to the AKI diagnostic protocol. The U.S. Food and Drug Administration (FDA) has authorized the marketing of the NephroCheck test. NephroCheck® is a commercial product combining two urinary biomarkers, TIMP-2 and IGFBP-7, to assess the risk of ARF.

Tissue inhibitor of matrix metalloprotease (TIMP-2) is a regulatory protein of 194 amino acids (21 kDa) with two domains: N-terminal and C-terminal. It reduces MMP activity and activates pro-MMP-2. The N-terminal domain (the first 125 amino acids) inhibits active MMPs by binding to their active site. This domain can change its conformation, affecting the binding affinity and specificity of the MMP. The C-terminal domain participates in pro-MMP-2 modulation. TIMP-2 forms a non-covalent bond with MMP-2 (gelatinase A) and is activated on the cell surface by interaction with MT1-MMP, which is required for collagenolysis and tissue remodeling. TIMP-2 is expressed in the glomeruli and tubular cells of the kidneys, regulating ECM components and maintaining the integrity of the kidneys. Its expression is regulated by cytokines and such growth factors as TGF-β and has been linked to fibrosis and kidney disease. TGF-β activates TIMP-2 expression via the Smad and MAPK pathways, increasing transcriptional activity and regulating ECM turnover. Other cytokines and growth factors, such as FGF and EGF, also affect the production of TIMP-2 but have been studied less [6].

Insulin-like growth factor 7 binding protein (IGFBP7) is a novel biomarker for predicting AKI that has gained attention as a biomarker in urine. IGFBP7 is highly expressed in the blood and urine of patients and mice with AKI through a c-Jun-dependent mechanism, correlating with renal dysfunction and programmed cell death. IGFBP7 originates from the epithelial cells of the renal tubules and acts as a biomarker and key mediator of AKI, inhibiting RNF4/PARP1-mediated tubular damage and inflammation [7].

TIMP-2 and IGFBP7 can be detected and measured using a variety of methods, including enzyme-linked immunoassay (ELISA), zymography, reverse transcription-polymerase chain reaction (RT-PCR), and surface plasmon resonance (SPR).

The study aimed to summarize published studies of TIMP-2 and IGFBP-7 early biomarkers to improve the diagnosis and prognosis of contrast-induced acute kidney injury.

Materials and methods: The analysis of articles indexed in the Pubmed, Web of Science, and Cochrane databases over the past 10 years has been conducted (Figure 1). We found 10 results in Pubmed and 3 in Web of Science for "contrast-induced nephropathy timp 2 igfbp 7" or "contrast-induced acute kidney injury timp 2 igfbp 7". 21 articles were selected after filtering. Most of the studies were conducted in America, China, and Europe.

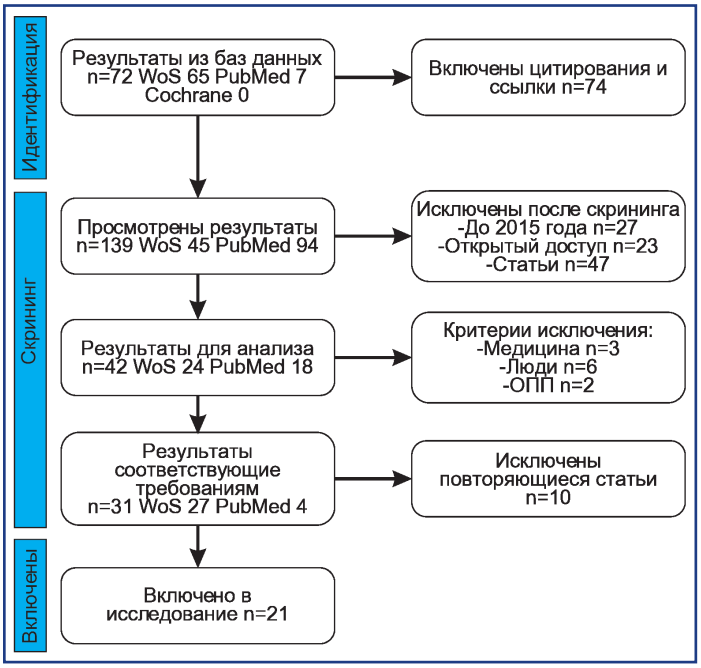

Figure 1 – Algorithm for selection of sources for analysis

Results: In the study by Q. Sun et al., the average dose of contrast medium was 3 ml/kg in 107 of the 137 children who received iodixanol injections. The mean volume was 2 ml/kg in the remaining 30 patients with heart disease who received yopamidol. The incidence of CI-AKI was 14.59% based on the SCr result [1]. In the CI-AKI group, urinary levels of NGAL, IGFBP-7, TIMP-2, and [IGFBP-7][TIMP-2] increased significantly at 2 and 6 hours and increased more rapidly than SCr, remaining high at 12 hours, in contrast to the group without CI-AKI. ROC analysis of CI-AKI diagnostics showed that [IGFBP-7][TIMP-2] was more effective for early diagnostics than IGFBP-7 or TIMP-2 alone. The authors note that the study is small and requires confirmation in multicenter studies. The lack of sensitive biomarkers for children with CI-AKI reduces the ability to intervene on time. Urinary NGAL, IGFBP-7, and TIMP-2 have shown sensitivity in CI-AKI diagnostics (Table 1) [1].

A. Breglia et al. noted that the incidence of CI-AKI was 3-fold higher in patients exposed to iopamidol than in those treated with iodixanol. There were no differences in age, sex, BMI, comorbidities, or use of nephrotoxic drugs [2]. The yopamidol group was exposed 4.5 times more than the iodixanol group, confirming a higher risk of CI-AKI [2].

Increases in IGFBP-7 and TIMP-2 after bypass surgery predicted a higher incidence of ARF in a study by A. Saad et al. Urine readings of these biomarkers predicted the development of ARF, protecting the kidney from tubular damage. Renal hypoxia developed in 50% in 24 hours; R2* levels rose but returned to baseline in 3 months. Patients with higher levels of TIMP-2 and IGFBP-7 responded better to revascularization. No sustained changes in serum creatinine or NGAL, KIM-1, TNF-α, IGFBP-7, or TIMP-2 levels were observed with ARAS [8].

Figure 2 shows an example of parametric maps after contrast imaging and renal stenting for a subject with ARAS at baseline and in 24 hours and 3 months. Maps obtained using the color scale for R2* demonstrate the development of transient widespread tissue hypoxia 24 hours after contrast imaging and renal stenting. This study was not randomized; people with diabetes were excluded, and most patients were men. Revascularization and contrast injection were performed as part of the same procedure. It did not allow the effect of each factor on hypoxia to be determined. The control group included patients with EH of similar age rather than "normal" people. Individuals with ARAS had lower GFR, and 30% had bilateral stenosis with extensive kidney damage. Levels of IGFBP-7 and

TIMP-2 in the renal veins, as well as NGAL, were elevated and inversely correlated with hypoxic changes in 24 hours in patients with chronic renal ischemia due to ARAS. Early hypoxic changes were transient and resolved in 3 months, highlighting the ability of the kidney to adapt to hypoxia even in elderly patients with low GFR. Among patients undergoing angioplasty, ARF was observed in 5.6% and subclinical ARF (increased lipocalin, without Cr increase) in 17.9%. Lipocalin levels remained elevated in one month in half of those with subclinical ARF [8].

Table 1 – Efficacy of uNGAL, ulGFBP-7, uTIMP-2 and [ulGBP7]*[uTIMP-2] biomarkers for the diagnostics of CI-AKI [1]

Area under the curve	Biomarkers			
	uNGAL	ulGFBP-7	uTIMP-2	[ulGBP7]* [uTIMP-2]
	0.718	0.779	0.779	0.811
CI 95%	0.575-0.860	0.658-0.901	0.650-0.908	0.681-0.941
Limit value	36.274	153.061	2.951	0.417
Sensitivity, %	0.70	0.80	0.75	0.80
Specificity, %	0.684	0.667	0.821	0.812

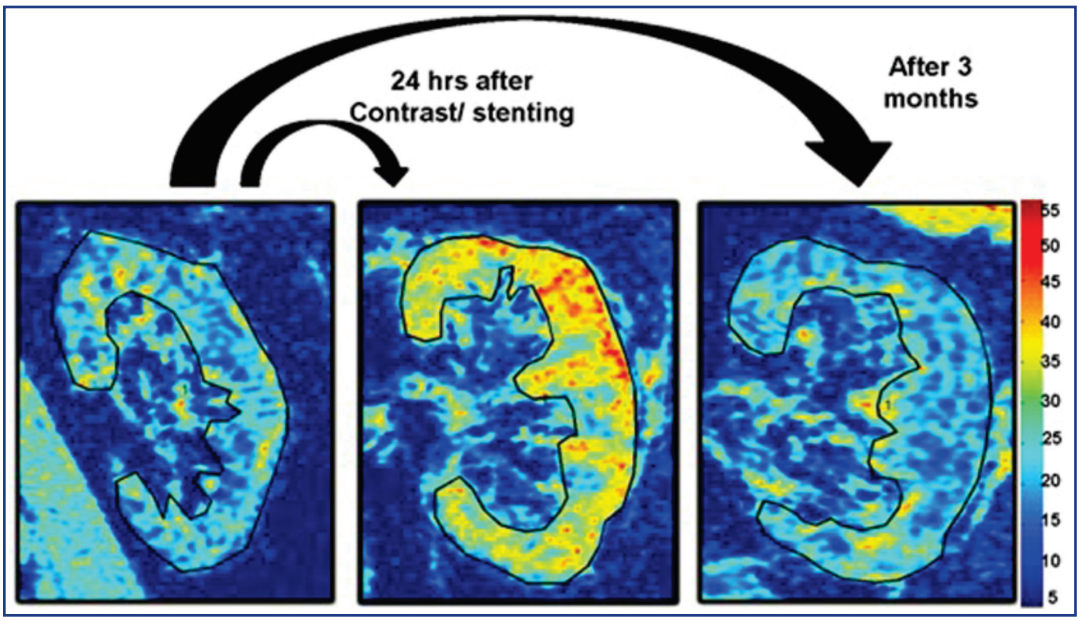

Figure 2 – Example of parametric maps [8]

A very interesting observation is made by S. Martin-Cleary et al.: after the marathon, serum creatinine increased by 40%, urinary TIMP-2 by 555%, and IGFBP-7 by 1094%. The values returned to baseline levels in 24 hours [9]. The PRESERVE randomized clinical trial "Prevention of Serious Adverse Events After Angiography" enrolled 922 participants who underwent coronary or non-coronary angiography at 53 health centers in the U.S., Australia, Malaysia, and New Zealand, making it the largest study to examine this marker in CKD patients undergoing angiography. 7.9% of the 922 participants in the study conducted by R. Murugan et al. developed CI-AKI, and 6.5% had adverse renal events by Day 90. The use of contrast medium was higher in patients who developed CI-AKI. There was no difference in the risk of death (2.7% versus 3.1%). 18% developed adverse events (persistent kidney dysfunction – 11% versus 2%). Patients with low GFR and high albumin-to-creatinine ratios had a high risk of adverse events. Thus, Stage 1 CI-AKI developed in 22% of them (vs. 7%). 46.7% of the 28 patients with adverse events died, 20% were on dialysis, and 43.3% had persistent renal dysfunction by Day 90. A high concentration of the [TIMP-2]•[IGFBP7] index was associated with a low risk of CI-AKI (aOR=0.59; P=0.002), but the predictive value of this index was low (AUROC=0.59). The [TIMP-2]•[IGFBP7] index was more sensitive and superior to other biomarkers for the early detection of ARF. Urinary levels of [TIMP-2]•[IGFBP7] did not increase after angiography in patients with mild ARF, indicating that cell cycle arrest is not the main factor in ARF [10]. This is confirmed in the study conducted by Rouve et al. [3]. It showed slight changes in [TIMP-2]•[IGFBP7] after exposure to the contrast medium.

According to R. Murugan et al. [10], the level of [TIMP-2]•[IGFBP7] may help in early risk stratification and rule out concerns about CI-AKI. A unique finding was a higher pre-angiographic urinary value [TIMP-2]•[IGFBP7] in patients without CI-AKI. This finding may be the result of chance alone or suggest that a higher pre-angiographic concentration of [TIMP-2]•[IGFBP7] in urine may

serve as a protection against the risk of CI-AKI, although the predictive accuracy of this index was low. The mechanisms associated with increased pre-angiographic urinary concentrations of [TIMP-2]•[IGFBP7] and a reduced risk of CI-AKI are unclear, and our findings require further confirmation in future studies. Limitations of this study included one-time urine and plasma collections, limited time intervals for biomarker assessment, and predominant male participation.

The Discovery Study showed that the urinary biomarkers - TIMP-2 and IGFBP7 are better predictive of the risk of ARF in critically sick patients than other biomarkers [11]. The combination of [TIMP-2]•[IGFBP7] and a furosemide (FST) stress test has also been shown to improve the prediction of ARF progression [12].

Biomarkers such as TIMP2•IGFBP7 appear to be a reasonable and effective method for early AKI prediction based on the analysis of existing studies. K.J. Gunnerson et al. showed high accuracy in predicting ARF based on a single measurement of urinary TIMP2•IGFBP7 after admission to the ICU [13]. M. Meersch et al. confirmed this biomarker's high sensitivity and specificity for ARF after cardiac surgery [14]. A study by K. Lakhal et al. also found that contrast-induced nephropathy was associated with higher mortality and the need for renal replacement therapy among patients who received contrast media [7].

The study conducted by E. Rouve et al. showed a significant increase in [TIMP-2]•[IGFBP-7] levels in 30% of patients after contrast media infusion, with 66% of them experiencing a worsening of KDIGO classification within 72 hours. However, the threshold of change in [TIMP-2]•[IGFBP-7] was not associated with CI-AKI, which may indicate the relative harmlessness of contrast agents [3].

Moreover, the incidence of ARF was similar in patients with STEMI who underwent angiography to that of the control group. This fact confirms the low incidence of ARF with contrast agents [10].

Other studies also support these findings. For example, [TIMP-2]x[IGFBP7] levels in a study with 42 participants were not significantly elevated in 4 hours after surgery and until the first day after surgery, highlighting the importance of measurement time for interpreting results [12].

Drug-induced nephrotoxicity is associated with 20% of ARF cases acquired in the hospital and 25% of ARF cases occurring in the ICU. Early detection of nephrotoxicity is critical, but TIMP-2 and IGFBP7 have not yet been used for these purposes outside of the ICU [12]. The toxic effect of ICM is minimal in ICU patients with multiple renal aggression. Disease severity and nephrotoxic load are risk factors for ARF independent of contrast agent infusion [15]. In a large study involving 6877 ICU patients (4351 with contrast, 2526 without contrast), after adjustments, ARF predisposition, dialysis, and mortality were not significantly higher in the contrast group in GFR >45. An increased risk of dialysis was observed with GFR ≤45 [11]. In another study, contrast administration was not associated with increased incidence of ARF, chronic kidney disease, dialysis, or transplantation at 6 months [16].

In the study by R.J. McDonald et al. [17], the ARF incidence was 5.0% (1059 of 21,346). The ARF incidence did not differ between the contrast (4.8%) and non-contrast (5.1%) groups; OR=0,94; P=0,38). In the "risk group" subgroups, the ARF incidence was higher in patients with a history of ARF, CKD, and CHF, but the differences were not significant for ARF (OR 1.10; P=0.36) or CHF (OR 1.18; P=0,18). After adjustment, the rate of emergency dialysis (OR 0.96; P=0.89) and short-term mortality (HR 0.97; P=0.45) was not different in patients who underwent computed tomography with and without contrast agents. Patients with AKI had a higher risk of dialysis (OR 15.75; P<0.0001) and mortality (OR 4.51; P<0.0001), regardless of the administration of the contrast agent. Besides, patients with high creatinine levels, diabetes, CHF, or renal dysfunction had higher rates of ARF, dialysis, and mortality regardless of contrast agent.

It can be noted that the results obtained by J.S. McDonald et al. [11, 18] are closely intertwined with the findings presented in S. Ehrmann et al. [15]. In particular, McDonald et al. showed that a reduced GFR was associated with an increased risk of ARF after computed tomography, and this risk was independent of the use of contrast, even with a GFR of less than 30 ml/min/1.73 m^2. This finding is reflected in a study by Ehrmann et al., where the AKI incidence was also similar between the contrast and control groups, with no significant difference (0%) observed. Moreover, both authors had comparable in-hospital mortality in the groups, highlighting no significant difference in outcomes when contrasting was used. The main risk factors, such as the assessment of sequential organ failure and the number of nephrotoxic agents used, were also similar in both studies. This calls into question the need to avoid contrast agents in patients with low GFR.

Discussion: Thus, the results of numerous studies confirm the feasibility of using biomarkers for the early diagnostics and prediction of CI-AKI and ARF. However, further multicenter studies must confirm these findings and address existing limitations. Early detection of nephrotoxicity remains critical, but TIMP-2 and IGFBP7 have not yet been used outside the ICU [12]. Clinical data show that intra-arterial injection of contrast agents is often associated with increased renal toxicity, but this belief is controversial and requires additional research [19]. It is also important to note the importance of hydration for the protection of the kidneys when using contrast agents [18].

ICMs are widely used in clinical procedures, increasing the risk of CI-AKI. Intensive care is the only supportive

agent in AKI, so new diagnostic approaches are required [5]. Daily measurements are not recommended, except in cases of a change in the clinical situation. Assessment of CI-AKI biomarkers, together with clinical information, should tailor the management of ARF to patients' individual needs. It will improve clinical practice and reduce the incidence of end-stage renal disease [17].

[TIMP-2] · [IGFBP7] predicts the development of severe ARF (KDIGO stage 2/3) with an area under the curve of 0.80-0.82. IGFBP7 predicts mortality, kidney recovery, and severity of ARF [20]. Increased [TIMP-2]·[IGFBP7] is associated with a composite endpoint of death or dialysis within 9 months. These markers can predict kidney damage, prompting closer monitoring of patients [21]. TIMP-2 increases earlier and longer than IGFBP7, as it is involved in cell cycle arrest, inflammation, and tubular regeneration after injury.

Conclusion Recent studies [1, 3, 8, 10, 11, 14] have shown the importance of early CI-AKI diagnostics using novel biomarkers such as IGFBP-7 and TIMP-2. Urine tests for these biomarkers allow CI-AKI detection much earlier than traditional methods based on serum creatinine levels. This finding has important implications for early intervention and improved patient outcomes.

Studies by Q. Sun et al. [1] and A. Saad et al. [8] demonstrate that using these biomarkers effectively diagnoses CI-AKI in children and post-bypass patients. At the same time, studies conducted by A. Breglia et al. show that the CI-AKI incidence is significantly higher in patients treated with iopamidol compared to iodixanol. This fact highlights the need to choose less toxic contrast agents [2].

The PRESERVE clinical trial confirms that the combination of TIMP-2 and IGFBP-7 is the most sensitive biomarker for early diagnostics and prediction of the CI-AKI risk [10]. Despite this fact, there are still unresolved questions, such as the mechanisms associated with the increase in the level of these biomarkers and their predictive accuracy, which requires further research.

Besides, a study by R.J. McDonald et al. [17] and J.S. McDonald et al. [11, 18] showed that the incidence of ARF does not differ between the contrast medium and non-contrast groups, indicating the need to consider other risk factors such as creatinine, diabetes, and heart failure. Patients with high creatinine levels, diabetes, chronic heart failure, or renal dysfunction have higher rates of ARF, dialysis, and mortality regardless of contrast medium use.

In general, the need for safer and more effective CI-AKI diagnostics and prevention remains relevant in Kazakhstan and abroad. Further multicenter studies will help improve the understanding and management of this serious complication.

Studies also highlight the importance of revascularization procedures and contrast media selection to minimize the CI-AKI risk in patients with chronic renal failure and other comorbidities. Closer follow-up of high-risk patients and tailoring the ARF management to patients' individual needs can significantly improve clinical practice and reduce the incidence of end-stage renal disease.

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АҢДАТПА

МЕТАЛОПРОТЕИНАЗА-2 ЗӘР ШЫҒАРУ ТІНІНІҢ ИНГИБИТОРЫНЫҢ (TIMP-2) ЖӘНЕ ИНСУЛИНГЕ ҰҚСАС ӨСУ ФАКТОРЫН БАЙЛАНЫСТЫРАТЫН АҚУЫЗ 7 (IGFBP-7) КОНТРАСТПЕН ТУЫНДАҒАН ЖЕДЕЛ БҮЙРЕК ЖАРАҚАТЫНДАҒЫ БОЛЖАМДЫҚ МӘНІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Бүйректің контрастты әсерінен жедел зақымдануы (БК-ӘЖЗ)контраст агенттерін қолданатын медициналық процедуралардың ауыр асқынуы болып табылады. Бүйректің жедел зақымдануы (БЖЗ) жиілігінің төмендеуіне қарамастан, (БК-ӘЖЗ) әсіресе төтенше жағдайларда бүйрек функциясының нашарлауының жетекші себептерінің бірі болып қала береді. Қан сарысуындағы креатинин (SCr) ерте диагностика үшін сенімді биомаркер болып табылмайды, өйткені оның деңгейі бүйрек массасының 50%-дан астамын жоғалтқанда ғана жоғарылайды. Заманауи йодталған контрастты заттар БЖЗ қаупін төмендетеді, бірақ созылмалы бүйрек ауруы және қант диабеті бар науқастар үшін қауіпті болып қала береді.*

Зерттеудің мақсаты *– TIMP-2 және IGFBP-7 ерте биомаркерлері туралы жарияланған зерттеулерді қорытындылау болды, бұл контрастпен туындаған жедел бүйрек жарақатының диагностикасы мен болжамын жақсарту.*

Әдістері: *Дереккөздерді іздеу Pubmed, Web of Science, Cochrane дерекқорларында жүргізілді. Шолу 2014 жылдан 2025 жылға дейін жарияланған 21 дереккөзді қамтиды.*

Нәтижелері: *ЙКЗ клиникалық процедураларда кеңінен қолданылады және БК-ӘЖЗ қаупін арттырады, қарқынды терапия жалғыз қолдау шарасы болып қала береді. [TIMP-2]·[IGFBP7] биомаркерлері жоғары сезімталдық пен дәлдікпен ауыр ЖБЖ (KDIGO 2/3 сатысы), өлім және ЖБЖ ауырлығының дамуын болжайды. Бұл биомаркерлердің жоғары деңгейлері 9 ай ішінде өлім немесе диализ қаупімен байланысты, бұл оларды пациенттерді мұқият бақылау үшін пайдалы етеді.*

Қорытынды: *Жақында жүргізілген зерттеулер IGFBP-7 және TIMP-2 биомаркерлерін пайдалана отырып, CI-AKI ерте диагностикасының маңыздылығын атап көрсетті, бұл ерте араласу және емдеу нәтижелерін жақсарту үшін маңызды. Кейінгі зерттеулер креатинин деңгейі, қант диабеті және жүрек жеткіліксіздігі сияқты қауіп факторларын ескере отырып, осы асқынуды түсіну мен басқаруды жақсартуға көмектеседі. CI-AKI диагностикасы мен алдын алудың қауіпсіз және тиімді әдістерінің қажеттілігі Қазақстанда да, шетелде де өзекті болып табылады. Тәуекелділігі жоғары емделушілерді мұқият бақылау және ЖРЖ басқаруын пациенттің жеке қажеттіліктеріне бейімдеу клиникалық тәжірибені жақсартуға және соңғы сатыдағы бүйрек ауруларының жиілігін төмендетуге мүмкіндік береді.*

Түйінді сөздер: *Металопротеиназа-2 зәр шығару тінінің ингибиторының (TIMP-2), инсулинге ұқсас өсу факторын байланыстыратын ақуыз 7 (IGFBP7), контраст-бүйректің жедел зақымдануы (ki-OPP); биомаркерлер.*

АННОТАЦИЯ

ПРОГНОСТИЧЕСКАЯ ЦЕННОСТЬ ТКАНЕВОГО ИНГИБИТОРА МЕТАЛЛОПРОТЕИНАЗЫ-2 (TIMP-2) МОЧИ И БЕЛКА, СВЯЗЫВАЮЩЕГО ИНСУЛИНОПОДОБНЫЙ ФАКТОР РОСТА 7 (IGFBP-7), В ОТНОШЕНИИ КОНТРАСТ-ИНДУЦИРОВАННОГО ОСТРОГО ПОВРЕЖДЕНИЯ ПОЧЕК: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Контраст-индуцированное острое повреждение почек (КИ-ОПП) – это серьезное осложнение медицинских процедур с использованием контрастных веществ. Несмотря на снижение случаев острой почечной*

недостаточности (ОПН), КИ-ОПП остается одной из ведущих причин ухудшения функции почек, особенно в неотложных ситуациях. Сывороточный креатинин (SCr) не является надежным биомаркером для ранней диагностики, так как его уровень повышается только при утрате более 50% почечной массы. Современные йодированные контрастные вещества (ЙКВ) снижают риск ОПН, но остаются опасными для пациентов с хронической болезнью почек и диабетом.

***Цель исследования** – обобщение опубликованных данных исследований ранних биомаркеров TIMP-2 и IGFBP-7 для улучшения диагностики и прогнозирования контраст-индуцированного острого повреждения почек.*

***Методы:** Проведен поиск источников в базах данных Pubmed, Web of Science, Cochrane. В обзор включен 21 источник, опубликованный с 2014 по 2025 гг.*

***Результаты:** ЙКВ широко используются в клинических процедурах и увеличивают риск КИ-ОПП, при этом интенсивная терапия остается единственным поддерживающим средством. Биомаркеры [TIMP-2]·[IGFBP7] предсказывают развитие тяжелой ОПН (стадия 2/3 по KDIGO), смертность и тяжесть ОПН с высокой чувствительностью и точностью. Повышенный уровень этих биомаркеров связан с риском смерти или диализа в течение 9 месяцев, что делает их полезными для тщательного наблюдения за пациентами.*

***Заключение:** Последние исследования подчеркнули значимость ранней диагностики КИ-ОПП с использованием биомаркеров IGFBP-7 и TIMP-2, что важно для раннего вмешательства и улучшения исходов лечения. Дальнейшие исследования помогут улучшить понимание и управление этим осложнением, учитывая факторы риска, такие как уровень креатинина, диабет и сердечная недостаточность. Необходимость в безопасных и эффективных методах диагностики и профилактики КИ-ОПП актуальна как в Казахстане, так и за рубежом. Тщательное наблюдение за пациентами с высоким риском и адаптация ведения ОПН к индивидуальным нуждам пациентов могут улучшить клиническую практику и снизить частоту терминальной стадии почечной недостаточности.*

***Ключевые слова:** ингибитор металлопротеиназы-2 (TIMP-2) мочи, белок, связывающий инсулиноподобный фактор роста 7 (IGFBP7), контраст-индуцированное острое повреждение почек (КИ-ОПП); биомаркеры.*

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MURAT TLEUGABYLULY, A PATHOMORPHOLOGIST, SCIENTIST, AND PROFESSOR

People say, "The height of the mountains will be visible as you move away from them." A year ago, Murat T. Aitkulov passed away. He has been a Candidate of Medical Sciences, a pathomorphologist of the highest category, associate professor, and a teacher who left an indelible mark in medicine.

He was born on April 10, 1941, in Saryozek village of Aiyrtau District of North Kazakhstan. In 1964, he graduated from the Karaganda Medical Institute (KMI) and studied for three years as a Graduate Student of the Pathological Anatomy Department. From 1967 to 1981, he worked as an Assistant at the Pathological Anatomy Department. He became an Associate Professor, held Teaching Training until 1995, and headed the Pathological Anatomy and Forensic Medicine Courses. From 1982 to 1997, he worked as a Deputy Dean of the Dentistry Faculty, then as Dean. From 1989 to 1992, he worked as a freelance pathologist for the Regional Health Department.

I know the son of Murat Tleugabiluly very well. He is a great teacher. He is patient, inner-world-minded, smart, reasonable, wise, intelligent, merciful, and wonderful.

When I worked at Korkyt Ata Kyzylorda State University as the Head of the General Medicine Department and Basic Valeology Department (1994-2006), I invited Murat Tleugabylovich as a very experienced teacher to conduct lectures and practical classes, and the State Examination for future Hygienists-Epidemiologists and Valeologists. Our Rector, Doctor of Technical Sciences, Professor Kylysh A. Bisenov, supported this intention, too. As our great Al-Farabi ancestor said, Murat Tleugabyluly, in addition to conducting lectures and educational work, made an excellent contribution to the quality of education of the young generation.

From 2011 to 2018, Murat Tleugabylovich continued his career at the Kokshetau Higher Medical College. In 2018, Murat Tleugabyluly started running the Morphology, Physiology, and General Pathology Department of the Medicine Faculty at Ualikhanov Kokshetau University.

He enormously contributed to the formation and structural strengthening of the immature faculty. During

his leadership, he initiated the development of the material and technical base, gave invaluable experience in the field of pedagogical skills, and became an indispensable mentor for the Department's staff.

The scientific interest of our well-known teaching staff is aimed at the topic of pulmonary pathology, so it is not surprising that the topic of the scientific work is selected from this direction. There are more than 70 publications on scientific and educational activities and many methodological manuals and textbooks.

Also, there is every reason to believe that Murat Tleugabyluly's contribution to the development and strengthening of the position of the state language in medical literature is invaluable. He translated selected textbooks on pathological anatomy into our native language, which are still relevant and are used in medical universities of the country. In addition, he published training manuals on Internal Diseases and Basic Methods for Diagnosing Internal Diseases in Kazakh.

For long pedagogical and educational activities, Murat Tleugabyluly was awarded the badges Excellence in Healthcare Worker of the USSR and Excellent Healthcare Worker of the Republic of Kazakhstan. In 1982, he was included in the Book of Honor of KMI. In 2001, He was awarded a letter of gratitude from the President of the Republic of Kazakhstan. Also, in 2018, he was awarded the Medal of Veterans of Labor for his contribution to the Development of KMI. Murat Tleugabyluly was an example of professionalism, hard work, and responsiveness. His professionalism, dedication, and sincere concern for the future of the young generation left an indelible mark on the hearts of his colleagues and students.

Certainly, a loved mate, a life partner, is the only reason for a man to convert a citizen's demands in life. He was lucky to have a loving wife, Nazym Akanovna, who honestly cared about Murat Tlegabyluly. She is a very intelligent and delicate person. These qualities of Nazym Akanovna are likely to bring honesty and stability to their family. She speaks the senior, modern desires of the Kazakh wife, fluent, competent, and literate. Her qualities seemed like Murat Tlegabyluly's, who inspires and stimulates.

My teacher did not succumb to the hardships of life. His diligence and perseverance were nurtured by his parents' accomplishments. I decided to write about children and grandchildren who descended from instructive souls to reveal this catchphrase, saying that they are born into the noble family and follow the path of the noble family. Children - Aizhan is a Dentist of the highest category, and Aidar is a Candidate of Biological Sciences, an Associate Professor of the Physiology Department at Buketov Karaganda University, a modern, capable of responding to the times promptly, educated, demanding innovative youth.

These good traditions in the family continued to the grandchildren of Murat Tleugabyluly. Olzhas graduated from the University, followed in his grandfather's footsteps, and taught at Karaganda Medical University; Adil graduated from Kokshetau and Astana universities and worked as an energy engineer. Asem is studying at the college as an artist-designer, and Amir is a student in the 9th grade. They are exemplary young people who grow up calm, deeply educated, and well-mannered. Children and grandchildren begin to recognize the signs and symbols inherent in talented people from early childhood, giving a modern direction to each child's inclinations while maintaining a Kazakh upbringing, growing up with the kindness and kindness of grandparents, the basis of their happy future. Therefore, it is proof of nobility that in the dynasty of Murat Tleugabyluly, the foundation of talented citizens who bear the name of our country is being laid.

We will always remember Murat Tleugabyluly, who contributed significantly to the development of education and medicine in Sary Arka and Syr, as a devoted, kind, great teacher and bright soul. His bright image will remain in our hearts.

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